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# Synthesis of Novel Boronated Amino Acids for BNCT an Alternate Cancer Therapy and Use of Microwaves in Organic Synthesis

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To the Graduate Council:

I am submitting herewith a dissertation written by Abhijit Achyut Naravane entitled "Synthesis of Novel Boronated Amino Acids for BNCT an Alternate Cancer Therapy and Use of Microwaves in Organic Synthesis." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

George W. Kabalka, Major Professor

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(Original signatures are on file with official student records.)

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# SYNTHESIS OF NOVEL BORONATED AMINO ACIDS FOR BNCT AN ALTERNATE CANCER THERAPY AND USE OF MICROWAVES IN ORGANIC SYNTHESIS

A Dissertation
Presented for the
Doctor of Philosophy
Degree

The University of Tennessee, Knoxville

Abhijit Naravane

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# DEDICATION

This dissertation is dedicated to my grandparents and my parents
Achyut and Amita Naravane

Who have loved and inspired me at all times in my life.
Without them, I simply could not have made it to here.

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# ABSTRACT

Boron neutron capture therapy (BNCT) is a binary form of cancer treatment wherein $^{10}B$ nuclei, when irradiated with thermal neutrons, produce high energy transfer particles. These particles, due to their size and energy, are confined to a radius of 9-10 μm, which is comparable to the size of single cell. Potential BNCT agents reported in the literature include boron-containing amino acids, nucleic acids, nucleosides, antibodies, and other biomolecules.

In recent years, microwaves have gained importance in organic chemistry. Microwave induced reactions are energy efficient, often enhance reaction rates, and generally lead to enhanced product yields. Recent studies have shown that potassium organotrifluoroborates offer solutions to a number of problems that sometime occur in organoboron coupling reactions.

This dissertation describes the synthesis of novel unnatural boronated amino acids as potential BNCT agents. The new microwave enhanced synthetic methodologies developed in this dissertation are important transformations in modern organic chemistry. Mild reaction conditions, short reaction times, and tolerance for various functional groups are advantages of these methodologies.

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## LIST OF SYMBOLS AND ABBREVIATIONS

| Symbol | Description |
|---|---|
| °C | Degree Celsius |
| γ | Weak gamma radiation |

| Abbreviation | Description |
|---|---|
| ACBC | 1-Aminocyclobutanecarboxylic acid |
| ACPC | 1-Aminocyclopentanearboxylic acid |
| BNC | Boron neutron capture |
| BNCT | Boron neutron capture therapy |
| BPA | 4-Dihydroxyborylphenylalanine |
| cm | Centimeter |
| DBDU | 5-(Dihydroxy)-2'deoxyuridine |
| DMF | Dimethyl formamide |
| DMSO | Dimethyl sulfoxide |
| DNA | Deoxyribonucleic acid |
| ECT | Emission capture tomography |
| g | Grams |
| h | Hours |
| Hz | Hertz |
| LET | Linear energy transfer |
| MeV | Mega Electron Volt |
| min | Minutes |
| mmol | Millimoles |
| mol | Moles |

| | |
|---|---|
| Tf | Trifluoromethanesulfonate |
| *N* | Normality |
| NCT | Neutron capture therapy |
| NMR | Nuclear magnetic resonance |
| PDT | Photodynamic therapy |
| RNA | Ribonucleic acid |
| THF | Tetrahydrofuran |
| TLC | Thin layer chromatography |
| 9-BBN | 9-Borabicyclo[3.3.1] nonane |
| $BF_3K$ | Potassium trifluoroborate |
| *n*-BuLi | *n*- Butyllithium |
| $CDCl_3$ | Chloroform-*d* |
| $^{13}C$ nmr | Carbon-13 nuclear magnetic resonance |
| CuI | Copper iodide |
| $d_6$ DMSO | Deuterated dimethylsulfide |
| GC | Gas Chromatography |
| $^{1}H$ nmr | Proton nuclear magnetic resonance |
| $H_2O$ | Water |
| *J* | Proton-proton coupling constant |
| $MgSO_4$ | Magnesium sulfate |
| $KHF_2$ | Potassium hydrogen fluoride |
| $Pd(dppf)Cl_2$ | [1,1'-Bis(diphenylphosphino)dichoropalladium(II) |
| $Pd(OAc)_2$ | Palladium acetate |
| TMS | Tetramethylsilane |
| GHz | Gigahertz |

**PART ONE**

# Synthesis of Novel Boronated Amino Acids for BNCT

# CHAPTER 1 INTRODUCTION

## 1.1.1 Boron Neutron Capture Therapy

Boron neutron capture therapy (BNCT)[1] is a binary form of cancer treatment in which a compound containing boron-10 ($^{10}B$) is selectively delivered to a tumor tissue prior to its irradiation by neutrons. The resulting activated $^{11}B$ nuclei (following the capture reaction) undergo prompt fission and release alpha-particles and high-energy lithium-7 ions. The linear energy transfer (LET) of these heavy charged particles has a range of approximately one cell diameter and thus they are lethal to the cells in which they are generated. The radiant energy of these particles thus does not have a significant effect on neighboring cells.[1,2] Boron-10 has a large neutron cross section and readily absorbs thermal neutrons.[3] The boron neutron capture reaction obtained with thermal neutrons is shown below.

$$^{10}_{5}B + {}^{1}_{0}n \longrightarrow \left[ {}^{11}_{5}B \right] \longrightarrow {}^{4}_{2}He\ (1.47\ meV) + {}^{7}_{3}Li\ (0.84\ meV) + \gamma\ (0.48\ meV)$$

Recent studies have shown that consumption of boron lowers the risk of prostate cancer by up to 64%.[4] Therefore, there is a growing interest in the synthesis of boron-containing compounds for potential use in medicine. As potential pharmaceutical agents, boron containing compounds have been used as enzyme inhibitors,[4] anti HIV agents, and for drug delivery.[5] Many classes of boron compounds have been synthesized and used in medicines and as BNCT agents.[6,7] These include boron containing amino acids,[8,9] hydantoins,[10,11] carbohydrates,[12,13] porphyrins,[14,15] nucleosides,[16,17] nucleotides,[16,17] nucleic acids,[16,17] liposomes,[18,19] lipoproteins,[20] antibodies,[21,22] immunoconjugates, [23,24] and other biomolecules.

This section of the dissertation deals with the synthesis of boron containing unnatural cyclic amino acids as potential BNCT agents for cancer treatment.

### 1.1.2 Unnatural Amino Acids for BNCT

It is believed that amino acids are preferentially taken up by growing tumor cells. Depending on the source of the boron, boronated amino acids can be divided into two categories: carboranes or boronic acids. The first carborane-containing amino acid, racemic *o*-carboranylalanine, was synthesized independently by Brattsev and Zakharkin.[25,26] Boronic acid based amino acids can be further divided into arylboronic acid and alkylboronic acid derivatives. 4-Dihydroxyborylphenylalanine (*p*-BPA) is one of the two BNCT agents used clinically.[27] Interest in the preparation of unnatural boronated amino acids stems in part from the positron emission tomography (PET) investigations carried out at the University of Tennessee on BNCT patients using both carbon-11 labeled 1-aminocyclobutanecarboxylic acid (ACBC) and fluorine-18 labeled BPA which revealed that cyclic amino acids localize in glioblastoma multiforme (a malignant brain tumor) more avidly than BPA.[28] The incorporation of boronated amino acids in tumor seeking peptides has also encouraged research on boronated amino acids.

### 1.1.3 Glioma: (Central nervous system tumor)

A brain tumor that develops from glial cells is called a glioma. It is a central nervous system (CNS) tumor that arises from glial cells. Gliomas most commonly affect the brain but they can also affect the spinal cord or any other part of the CNS, such as the optic nerves. All current forms of therapy, including surgery, chemotherapy, radiotherapy, immunotherapy, gene therapy and combined approaches can not be used to treat high-grade gliomas, and specifically glioblastoma multiforme.[29] Five year survival rates for patients diagnosed with glioblastoma multiforme in the United States are less than a few percent.[30,31] Chemotherapy and radiotherapy are not very effective for high-grade gliomas

due to their failure to destroy microinvasive tumor cells within the brain. Recent molecular genetics studies have revealed that the problem is complex.[32] The challenge is to selectively target tumor cells, with little or no effect on normal cells and tissues adjacent to the tumor. BNCT can provide a way to achieve this goal by selectively destroying malignant cells while not destroying normal cells.

# CHAPTER 2 LITERATURE REVIEW

## 1.2.1 Boron Neutron Capture Therapy

This section describes the origin, background, and current developments in the field of boron neutron capture therapy (BNCT). The concept of BNCT was introduced in 1936 as a new technique to overcome some of the limitations of cancer therapies available at that time.

### 1.2.1.1 Present-Day Therapies of Cancer

Drawbacks in the existing therapies for cancer have led to the development of new methods for treating the disease in a more effective manner.[2] In the case of most cancer involving solid tumors, surgical removal of the malignant tumor is the preferred method of treatment. However there is always an uncertainty as to whether or not all malignant cells have been removed. Residual malignant cells can become the foci for tumor recurrence either at the original site of tumor or at other locations; it can also lead to it spreading to other locations. Radiotherapy, chemotherapy, immunotherapy, gene therapy and surgery do not provide complete solutions.[33] Despite aggressive treatment using combinations of therapeutic modalities, effective results have not been achieved in most cases. The challenge in the development of a new cancer therapy lies in the ability to destroy all malignant cells without destroying nearby normal cells. In both chemotherapy and radiotherapy, adjacent normal cells are destroyed during the treatment of malignant cells. The dose required to destroy cancer cells is enormous which can affect nearby cells.

### 1.2.1.2 Basis and the Development of Binary Systems for Cancer Treatment

There are several binary systems now in various stages of development; these include photodynamic therapy, photon activation therapy, radiation sensitizers, gene therapy, and neutron capture therapy (NCT). The need for selective and specific destruction of cells has led to the development of these binary therapies.[1,2] They involve the use of two components for the treatment of cancer. Each individual component is relatively harmless to cells but their combination produces lethal effects. For this approach to be successful it is very important that at least one component be limited specifically to tumor cells while second component may be exposed to all cells in particular area.

### 1.2.1.3 Principle of Neutron Capture Therapy

The basis of neutron capture therapy is the fact that the nuclei of certain nuclides, both radioactive and non-radioactive, readily absorb thermal neutrons.[34] Non-radioactive nuclides are used in NCT.[2] The technique is most commonly referred as boron neutron capture therapy (BNCT) when boron-10 is used. BNCT is a binary radiation therapy which brings together two components, the first component is a stable isotope of boron (boron-10) that can be concentrated in tumor cells by attaching it to tumor specific agent. The second is a beam of low-energy neutrons. BNCT requires selective delivery of large quantities of boron-10 to the tumor (> 15 ug boron per g tumor).[35] After deposition of the boron-10, the area is irradiated with a beam of low energy neutrons. Following neutron capture, the activated boron-11 annihilates which results in the formation of two high energy species, a lithium ion and an alpha particle. The linear energy transfer (LET) of these heavy charged particles has a range of approximately one cell diameter and thus they are lethal to the cells in which they are generated.

### 1.2.1.4 Basis for the Choice of Boron as a Nuclide in Neutron Capture Therapy

There are a number of nuclides that have a high capacity for absorbing thermal neutrons; among them, $^{10}B$ is the most attractive for the following reasons: 1) it is not radioactive but is readily available, comprising approximately 20% of naturally occurring boron; 2) the particles emitted by the capture reaction are largely high linear energy transfer (LET); 3) the particles have combined path lengths in the range of approximately one cell diameter and thus they are lethal to the cells in which they are generated; and 4) $^{10}B$ has a high cross section of 3838 barns (1 barns = $10^{-24}cm^2$) for thermal neutrons.[3,36] This value is large by nuclear standards and exceeds the value for tissue elements like carbon, hydrogen, and oxygen by at least two orders of magnitude. Due to its small atomic size, boron can replace carbon in many organic structures, generating compounds biologically similar to those compounds from which they were derived. Much of the work in the area of compound development for NCT has focused upon use of boron-10.[2]

### 1.2.1.5 History and Development of the Concept of BNCT

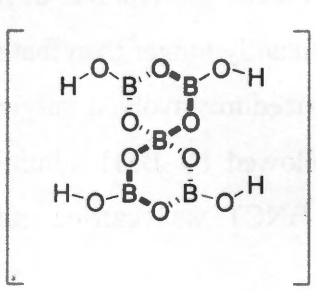
The main idea behind BNCT as a means of destroying tumors was actually proposed shortly after discovery of neutrons in 1932.[37] Because neutrons are electrically neutral they can readily penetrate the charged field of an atomic nucleus. This can trigger a fission reaction, causing the nucleus to break apart, releasing radiation. The disintegration of certain nuclei due to capture of thermal (or slow) neutrons was first observed by Fermi and others. [38] In 1935, Taylor described the capture of thermal neutrons by boron-10 nuclei followed by production of lithium ion and an ά-particle.[39] From these demonstrations, in 1936 Gordon Locher of the Bartol Research Foundation of the Franklin Institute in Philadelphia, Pennsylvania first pointed out the idea of treating cancer with the radiation released after absorption of neutrons by boron-10.[34] His concept called upon a simple neutron capture reaction by boron for a binary method in which a boron-10 in the compound that specially localizes in the tumor cells and thermal (or

slow) neutrons would be the two components of binary system; a lithium ion and an ά particle would then be the cytotoxic energetic products. Early attempts to cure cancer using Lochers concept were unsuccessful due to the non-selective uptake of the boronated agents available at the time and a lack of appropriate neutron beams.[40]

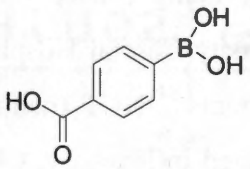
The first clinical trials took place in 1954 when L. E. Farr of Brookhaven National Laboratories and William H. Sweet of the Massachusetts General Hospital treated malignant brain tumors using $^{10}B$ enriched sodium borate as capture agents.[41,42] Five patients received a single radiation dose and five received multiple fractionated dose. These trials were not successful because of the inadequate tumor specificity of the boron compound that had been used, insufficient tissue penetrating properties of the thermal (or slow) neutron beam, and high concentrations of boron in blood when compared to the tumor.[43]

As noted, during the 1950s and early 1960s, boric acid and its derivatives were used in clinical trails.[44] The structures of these compounds are shown in Figure 1.2.1. Since the 1960s, significant advances have been made in the development of tumor specific boronated agents and also in the modification of nuclear reactors that can supply neutrons of appropriate energy. During this time, the polyhedral borane anions $B_{10}H_{10}^{-2}$ and $B_{12}H_{12}^{-2}$ were discovered.[45,46] Also, icosahedral carboranes *closo*-1,2- and *closo*-1,7-$C_{12}B_{10}H_{12}$ were synthesized.[47] These compounds were very attractive for BNCT due to their remarkable stability. 4-Dihydroxyborylphenylalanine and disodium mercaptoundecahydro-*closo*-dodecaborate emerged as promising BNCT agents.

In 1967, Japanese neurosurgeon Hiroshi Hatanaka initiated clinical trials with brain tumor patients using a thermal neutrons and $^{10}B$-enriched sodium mercaptoundecahydrododecaborate ($Na_2{}^{10}B_{12}H_{11}S$).

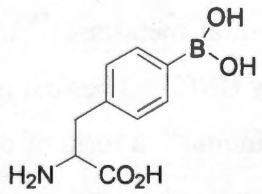



Boric acid
$B(OH)_3$



PCPB

p-Carboxyphenyl-
boronic acid



BPA

p-Boronophenyl-
alanine

Figure 1.2.1 Compounds used in the initial trials for BNCT

The early clinical results revealed a mean survival rate of forty four months for the thirty-eight patient tested; this was significantly longer than that obtained by chemotherapy and radiation therapy.[48] Hatanaka's procedure involved surgical removal of as much of the tumor as possible which was followed by BSH administration via a slow infusion. Twelve to fourteen hours later, BNCT was carried out at one of several available reactors.[49]

Hatanaka's results generated strong interest in BNCT. Clinical trials are now continuing in Japan. Beginning in 1994, several clinical trials were initiated in the United States and Europe.[50-52] Clinical trials are now being carried out in Sweden and Finland.[53] The clinical team at the Helsinki University Central Hospital and VTT (Technical Research Center of Finland) now accept patients.[54] NCT (neutron capture therapy) and neutron sources are currently being constructed in Hungary, China, Taiwan, Thailand and South America.[55]

### 1.2.1.6 Other Types of Tumor Treated by BNCT

Clinical interest in BNCT lies primarily on treatment of high-grade gliomas[56] as well as either cutaneous primaries[57] or cerebral metastases[58] of melanoma. Recently, two other types of cancer have been treated by BNCT. The first is recurring tumors of the head and neck.[59] The second is an adenocarcinoma,[60] a form of cancer that originates in glandular tissue of the colon that had metastasized to the liver. Using new procedures, several groups are now exploring the possibility of treating metastatic tumors of the liver.[61, 62]

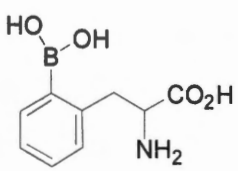
### 1.2.1.7 Potential BNCT Agents

The clinical success of BNCT depends upon the following factors: 1) selective delivery of a sufficient quantity (~15-30 mg per gram of tumor tissue) of a non-toxic $^{10}B$ containing compound; 2) an ability to target tumor cells selectively in the presence of normal cells; and 3) a neutron flux sufficient to achieve the nuclear reaction.[1, 2]

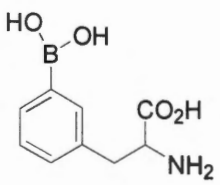
During the early years of development of BNCT, only compounds were considered that were either commercially available or easily prepared. Though BPA and BSH are used in clinical trials, many research groups are working on the synthesis and design of various classes of tumor specific boronated compounds. Some of the compounds being studied are described below.

**Amino Acids**

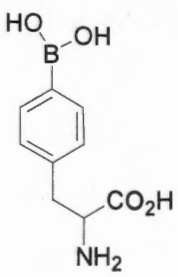
Various research groups have examined boron containing amino acids because of the fact that 4-dihydroxyborylphenylalanine (BPA) is one of the two clinically used BNCT agents. *Ortho* and *meta* isomers[63,54] of BPA have been synthesized and evaluated as BNCT agents. The *para*-isomer of BPA[65,66] has also been synthesized. Dihydroxyboryl analogues of phenylalanine are shown in Figure 1.2.2. A serious drawback related to BPA and its derivatives is their low water solubility. The solubility of BPA can be enhanced by complexation with a monosaccharide like glucose.[67-69] Thus, administration of BPA is generally carried out using an aqueous solution containing fructose, which converts BPA to a mixture of water-soluble borate complexes. In order to increase the solubility of BPA, hydrophilic groups such as hydroxyl groups have been attached to its structure as shown in Figure 1.2.3.[70,-72] Carboranes contain a higher percentage of boron and many different carborane containing amino acids have been synthesized and evaluated as potential BNCT agents.[73-75] Some of these boronated amino acids are shown in Figure 1.2.4. In past years, our research group has synthesized a variety of novel non-natural boronated cyclic amino acids.[76]




*ortho* -BPA




*meta*-BPA




*para*-BPA

Figure 1.2.2 Analogues of BPA

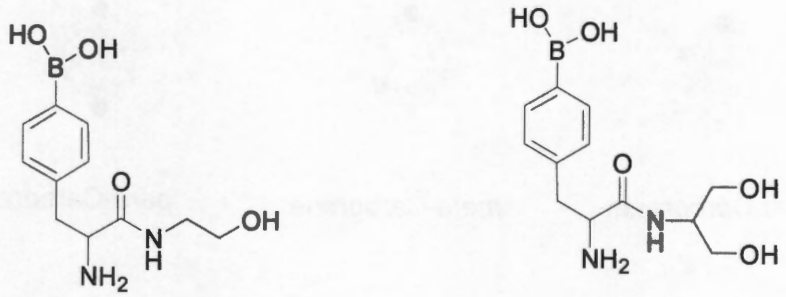
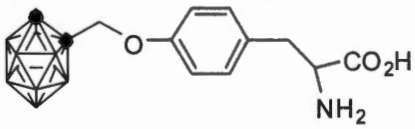


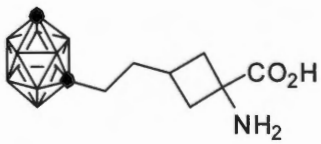

Figure 1.2.3 Hydrophilic derivatives of BPA

*ortho*-Carborane

*meta*-Carborane

*para*-Carborane




● = CH

Vertices = BH

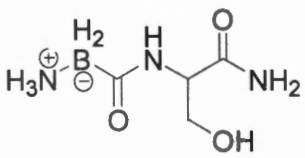
Figure 1.2.4 Carborane containing amino acids

**Boron Containing Peptides**

Boron containing peptides have also been synthesized due to the possibility that small peptides can cross cellular membranes and be utilized by tumor cells. There has been emphasis on development of peptides containing polyhedral borane anions. Boronated di- and tri-peptides derived from zwitterionic boron containing amino acids analogues are shown in Figure 1.2.5[77]

**Nucleosides, Nucleotides, and Nucleic Acids**

Several boronated analogues of the biochemical precursors to nucleic acids, including nucleosides, and nucleotides have been synthesized and evaluated as potential BNCT agents.[77-80] Compounds in this class usually contain a sugar residue, a base, and a phosphoric acid. Nucleosides do not have the phosphoric acid moiety.[81] These compounds, due to their importance in the building blocks of cells, are studied widely as potential BNCT agents. Compounds, such as the 3-(dihydroxypropylcarboranylpentyl)-thymidine derivative N5-2OH, have shown low toxicities and selective tumor cell uptake.[82,83] It has been thought that the effectiveness of BNCT would be increased by introducing boron into the cell nucleus via DNA.[84] This idea led to the synthesis of the first boronated nucleoside, 5-(dihydroxyboryl)-2'-deoxyuridine (DBDU).[85-67] Numerous carboranes and boron containing nucleoside derivatives were synthesized, structures of some of them are shown in Figure 1.2.6.[88,89] Along with nucleosides, boron containing nucleotides have also been synthesized and biologically evaluated.[90,91]



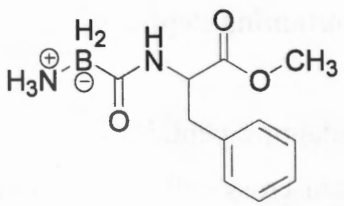
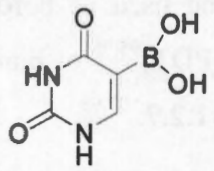
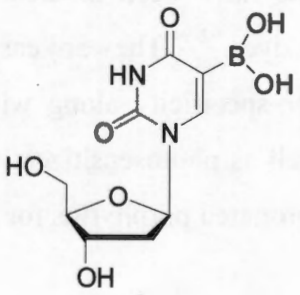



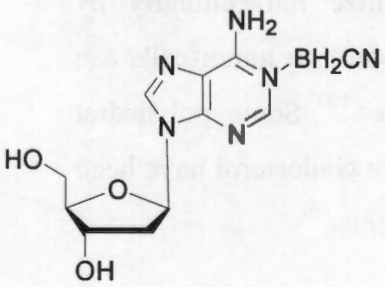

Figure 1.2.5 Boron containing peptides




5-(dihydroxyboryl)uracil




5-(dihydroxyboryl)-2'-deoxyuridine
DBDU



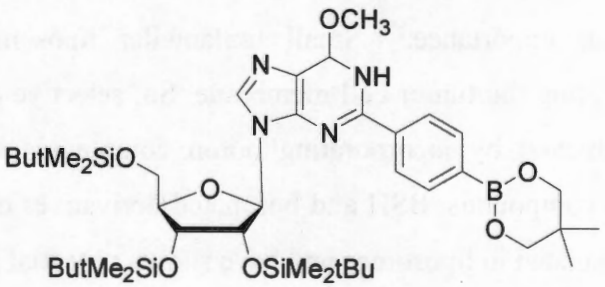




Figure 1.2.6 Boron containing nucleic acid and bases and nucleosides

**Porphyrins**

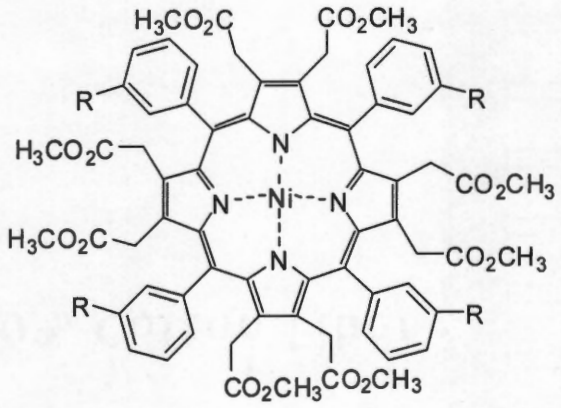
Porphyrins are a very important class of compounds in biological systems. Boron-containing porphyrins have been studied widely due to their low systemic toxicity compared with other dyes.[92-94] They are easy to synthesize. Boron-containing porphyrins have excellent tumor specificity along with the fact that they can be used as boron delivery agents as well as photosensitizers for photodynamic therapy (PDT)[95,96] of brain tumors. Important boronated porphyrins for BNCT are shown in Figure 1.2.7. [97,98]

**Liposomes**

Liposomes are spherical lipid bilayers that form in aqueous media, Figure 1.2.8. Due to their affinity for cancerous tissues, they are used for delivery of polar molecules of medical importance.[99] Small unilamellar liposomes can localize intracellularly by penetrating the tumor cell membrane. So, selective delivery of boron to tumor cells can be achieved by incorporating boron compounds into liposomes.[100] Some polyhedral boron compounds, BSH and boronated derivatives of steroids like cholesterol have been encapsulated in liposomes and have shown potential as BNCT agents.[101]

**Carbohydrates**

A major issue with some boronated compound used for BNCT is solubility, incorporation of carbohydrates into the boronated compound increases the solubility. Carbohydrate compositions of malignant cells differ from those of normal cells.[102] It is believed that high concentrations in tumors, through glucose transport, can be achieved.[103] Many boron and carborane containing analogs of glucose, mannose and ribose have been synthesized. Carborane containing analogue of carbohydrate is shown in Figure 1.2.9.[88,104]




R= $-OCH_2CB_{10}H_{10}CH$

Figure 1.2.7 Carborane-containing porphyrins

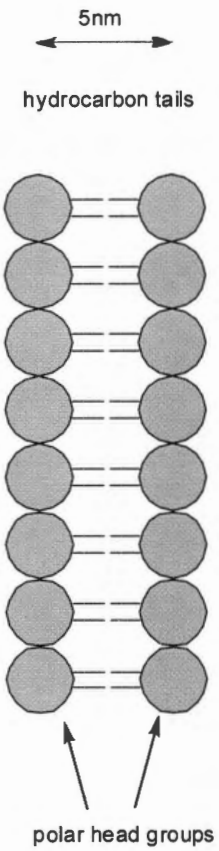



Figure 1.2.8 Lipid bilayers of a liposome

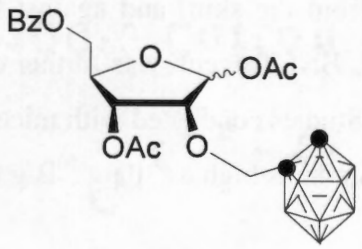



Figure 1.2.9 Carborane containing analogue of carbohydrates

### 1.2.2 Unnatural Cyclic Amino Acids

This section deals with non-naturally occurring cyclic amino acids and our rational for their choice as potential BNCT agents. A brief overview of the history and development of boronated amino acids as potential BNCT agents is also presented

#### 1.2.2.1 4-Dihydroxyborylphenylalanine (BPA)

BPA was first reported in 1958; it is one of the two amino acids used in BNCT trials in the United States.[105] Work in the area of BNCT using BPA began intensively when studies using neutron irradiation experiments found BPA to be potent against B-16 melanoma (malignant tumors arising from the skin) and against Green's melanoma in hamsters.[106] The usefulness of BPA as a BNCT agent was further demonstrated by work with melanoma in pigs and humans.[107] Studies conducted with mice showed $^{10}B$-enriched BPA achieved tumor concentration of boron as high as 30 μg $^{10}B$/g tumor.[108]

The low solubility of BPA in water has been a major problem in its use. This problem has been overcome by converting BPA to more water soluble complexes such as boronate esters with carbohydrates, diethanolamine, and cyclodextrin derivatives. In recent clinical trials with melanoma patients, BPA-fructose complexes have shown selective tumor uptake and good tumor to blood boron concentration ratios.[109] BPA has also been shown to accumulate in brain tumors and has been proposed for treatment of brain cancer.[110] The most significant feature of BPA is its ability to cross the blood brain barrier. Studies conducted on mouse brain models with fructose-PBA complex have shown that neutron capture therapy with BPA is a safe procedure for brain cancer.[111] Studies of BNCT for treatment of rat brain tumor have shown that the brain and blood vessels of rats subjected to BNCT were normal and intact without any damage to surroundings tissue.[112,113.] In contrast brains of X-ray radiation survivors showed loss of neurons, slowing of brain growth, and serious intellectual deficiencies.

Clinical trials with BPA for BNCT of human malignant melanoma in Japan suggested that the success of BPA against melanoma is based on the fact that the melamine pigment is synthesized *in vivo* from phenylalanine and tyrosine.[114] It is also know that melanoma cells incorporate both phenylalanine and tyrosine from extracellular fluid.[115] Several studies have been conducted to examine the pharmokinetics of $^{10}$B-BPA. Melanoma studies were conducted using $^{18}$F labeled BPA and the selectivity of $^{18}$F-labeled BPA for melanoma tumors was up to 8 times higher than those of normal tissue.[116]

### 1.2.2.2 Amino Acids other than BPA

As noted earlier boric acid and some of its derivatives were used as delivery agents, but these compounds had poor tumor retention, and attained low tumor/brain ratios.[117] *S*-(2-boronoethyl)cysteine was the first alkylboronic acid to be reported (Fig. 1.2.10 ).[118] This compound was disappointing as a BNCT agent. Several cyclopentane and cyclohexane containing boronated unnatural amino acids have been prepared and used in biodistribution studies.[119,120] L-Carboranylalanine (Figure 1.2.11) is currently undergoing *in vivo* and *in vitro* studies.[121] Other compounds such as the ammonium carboxyborane analogue of glycine have been synthesized for use in BNCT.[122] Various derivatives of BPA and other boron-containing amino acids, such as glycine, alanine, aspartic acid, tyrosine, cysteine, and nonnaturally occurring amino acids have also been synthesized.[123-127] Carborane containing amino acids have been synthesized in an attempt to deliver higher concentrations of boron to tumors without increased toxicity.


Figure 1.2.10 Alkylboronic acid amino acids

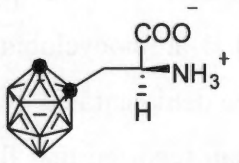
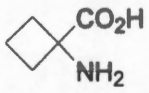


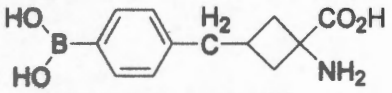

Figure 1.2.11 L-carboranylalanine

### 1.2.2.3 1-Aminocyclobutanecarboxylic Acid (ACBC) and its Derivatives

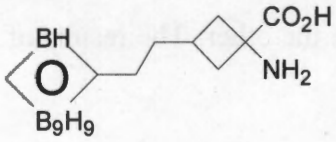
Several studies have been conducted with ACBC which has been shown to be preferentially retained in intracerebral tumors.[28,114] PET (positron emission tomography) investigations using carbon-11 labeled 1-aminocyclobutanecarboxylic acid (ACBC) carried out at the University of Tennessee demonstrated that this amino acid localizes in tumors more avidly than BPA.[28] Goodman reported that fluorine-18 labeled 1-amino-3-(fluoromethyl)cyclobutanecarboxylic acid and its derivatives also localized in tumors.[133] Because of this, many research groups have synthesized boronated cyclic unnatural amino acids as potential BNCT agents. However it is known that boronic acids have low lipid solubility which is not favorable for tumor-brain boron distribution ratios.[126] Our research group has synthesized various boronated cyclic unnatural amino acids as potential BNCT agents.[128-130] We suggested that replacement of a phenyl group with an alkyl linker might increase the water-solubility. We reported the synthesis of series of 4-dihydroxyborylphenyl derivatives of ACBC.[131] *m*-Carborane containing ACBC derivatives and a less lipophilic *nido* derivative were also synthesized.[76,132] Due to their high boron content and chemical stability, carboranes were thought to be advantageous. However the use of *m*-carboranyl derivatives for BNCT is limited *in vivo* due their hydrophobic nature. *Nido* derivatives show good water solubility but, due to the ionic character of the cage, they can not be used effectively *in vivo* because of non-specific protein binding. To overcome this problem, our group has synthesized water soluble polyol containing *m*-carboranyl ACBC derivatives.[133] To increase water solubility, carbohydrates like galactose have been incorporated into the carborane cage.[134] Some of the compounds are shown in Figure 1.2.12. For these reasons, we have focused our attention on the development of non-naturally occurring amino acids. Most compounds prepared to date have been derivatives of ACBC. We have also prepared boronated cyclopentane- and cyclohexaneamino acids derivatives for biodistribution studies.[119,120.]



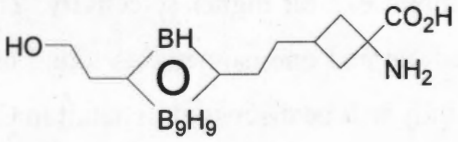

ACBC



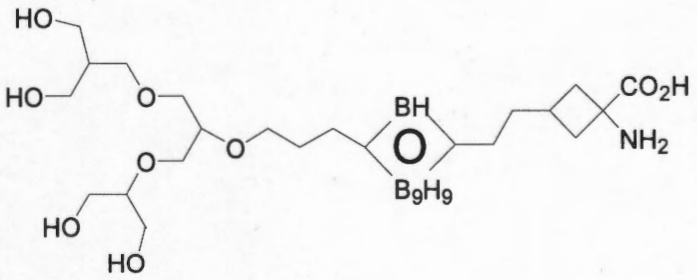

4-dihydroxyboryl analogue of ACBC



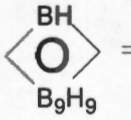

*m*-carboranyl analogue of ACBC




*m*-carboranyl analogue of ACBC




Polyol derivative of *m*-carboranyl analogue of ACBC




= *meta*-carborane

Figure 1.2.12 ACBC and its derivatives

### 1.2.2.4 1-Amino-3-dihydroxyborylcyclopentanecarboxylic Acid

The five-membered ring analogue, 1-amino-3-dihydroxyborylcyclopentanecarboxylic acid, demonstrated high tumor selectivity; exhibiting a nearly 22:1 ratio of tumor to brain boron concentration.[135] The tumor to blood and tumor to skin ratios were also somewhat high. The amino acid prepared was a diastereomeric mixture therefore it is thought that a single diastereomer of 1-amino-3-dihydroxyborylcyclopentanecarboxylic acid might exhibit higher selectivity. The separation of this diastereomeric mixture was carried out and one isomer was found to be more effective than the other. The results of this study will be discussed in detail in Chapter 3.

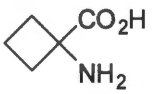
# CHAPTER 3 SYNTHESIS OF BORONATED UNNATURAL CYCLIC AMINO ACIDS

## 1.3.1 Research Objective

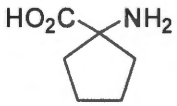
This part of the dissertation focuses on the syntheses of derivatives of boronated cyclopentanecarboxylic acids and separation of the diastereoisomers of 1-amino-3-dihydroxyborylcyclopentanecarboxylic acid (ACPC). Boronated cyclobutanecarboxylic amino acids have also been synthesized. Structures of ACPC and ACBC are shown in Figure 1.3.1. In this chapter the syntheses of five- and four-membered boronated unnatural cyclic amino acids are described. The synthesis and separation of diasteriomers of 1-amino-3-dihydroxyborylcyclopentanecarboxylic acid is also illustrated.

## 1.3.2 Rationale for the Choice of the Structures of Target Molecules

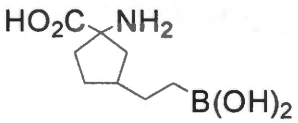
The structures of the target molecules were chosen based on preliminary biological results obtained using 1-amino-3-dihydroxyborylcyclopentanecarboxylic acid (ACPC), a boronic acid shown in Figure 1.3.1. Based on the fact that ACPC demonstrated high tumor selectivity, exhibiting a nearly 22:1 ratio of tumor to brain boron concentration.[135] We decided to synthesize derivatives of boronated cyclopentaneaminocarboxylic acids and carry out the separation of the diastereiomers. Substituted ACBC derivatives had been synthesized earlier for *in vivo* biodistribution evaluation.[136] To complete a structure–activity relationship study (by adjusting the lipophilicity of the compounds), we also prepared 3-ethylboronic substituted ACBC. Structures of our target molecules are shown in figure 1.3.2.




ACBC

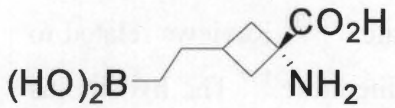



ACPC

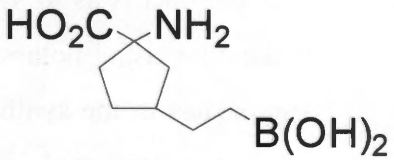



Boronic acid derivative of ACPC

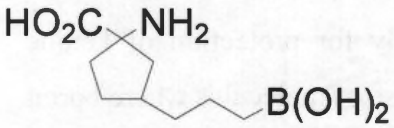
Figure 1.3.1 ACBC and boronic acid derivative of ACPC



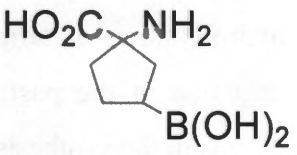

A




B




D




C

Diastereoisomers of C

Figure 1.3.2 Structures of target molecules

### 1.3.3 GENERAL Strategy for the Synthesis of Boronated Cyclopentane and Cyclobutane Amino Acids.

Hydantoins are precursors for α-amino acids and they are readily prepared from ketones. Our approach was to synthesize ketone moieties which could be readily converted into hydantoins using potassium cyanide and ammonium carbonate.[137,138] Reviews related to approaches to the synthesis of hydantoins can be found in literature.[139] The hydantoins were then converted into amino acids by hydrolysis with sulfuric acid. There are several reports dealing with the introduction of boron on to a ring.[140] In some of the targeted boronated cyclic amino acids, the boron is not directly attached to the ring. From previous studies, we knew that hydroboration of terminal alkenes in the presence of a hydantoin could be achieved.[141] Thus we decided to introduce boron through the hydroboration of terminal alkenes. The ketone moiety can be protected using various reagents; in the past, 1,2 hexanediol was used successfully for protection of ketone groups in the synthesis of boronated amino acids.[142] In the case of molecules where boron is directly attached to the ring, we decided to introduce boron via reactions using diboron reagents such as bis(pinacolato)diboron. Diboron reagents are useful for borylation of unsaturated organic compounds and organic halides.[143,144] In recent years, 1,4-addition reactions of diboron reagents with α,β-unsaturated carbonyl compounds have been achieved using copper[145] and platinum[146] catalysts. Since hydrolysis of hydantoins produces α–amino acids, it was decided to utilize hydantoins as precursors to the derived α–amino acids moiety.[147 148]

### 1.3.4 Synthesis of Compound A

1-Amino-3-[(dihydroxyboryl)ethyl]cyclobutanecarboxylic acid, **A**, was synthesized from but-3-enyloxymethylbenzene[149] as outlined in Scheme 1.3.1. We decided to use a [2+2] cycloaddition reaction to construct the 3-substituted cyclobutanone skeleton. Cyclobutanone **2** was obtained by the cycloaddition of but-3-enyloxymethylbenzene with dichloroketene, which was formed *in situ* from trichloroacetyl chloride in the presence of a zinc–copper couple and phosphorous oxychloride. Due to the unstable nature of cyclobutanone **2** during silica gel column chromatography, the crude product was used directly in the next step. Reductive dechlorination of **2** was achieved with zinc in acetic acid to produce cyclobutanone **3**. In our previous work, we found that cyclobutanone ethanediol ketals were unstable when compared to the corresponding 1,2-hexanediol derivatives; so we decided to carry out the protection of ketone moiety in compound **3** with 1,2-hexanediol.[150] We felt that, due to the volatile nature of intermediates **6** and **7**, it would be best to use 1,2-hexanediol for protection purposes. Since ketal **4** exists in a spiro configuration and contains two stereogenic centers, diasteriomers are formed in 1:1 ratio. The resonance of the carbons at the spiro core are clearly visible in the $^{13}$C-NMR spectrum. Hydrogenation of ketal **4** (10% palladium on charcoal) in methanol at room temperature resulted in formation of **5** in good yield. Bromination of **5** using $CBr_4/PPh_3$ in dichloromethane at room temperature gave 3-(bromoethyl)cyclobutanone acetal, **6**.[151] The dehydrobromination of **6** to generate the alkenyl group was carried out using NaOH in polyethylene glycol (PEG-600).[152] The ketal group in **7** was removed using dilute hydrochloric acid in refluxing ethanol, which gave ketone **8**. Due to the highly volatile nature of **8**, it was used directly for the Bucherer–Strecker reaction.[139] Crude **8** was converted to hydantoin **9** using potassium cyanide and ammonium carbonate. The reaction produced hydantoin **9** in good yields. The boronic acid group was introduced in a stepwise manner; first carrying out the hydroboration of **9** with 3.0 equivalents of

diisopinocampheylborane ($Ipc_2BH$) in THF at room temperature. The resultant diisocampheylborane product was converted to boronic acid **10** by reaction with acetaldehyde and then aqueous HCl according to the literature procedure.[153] The amino acid was formed by hydrolyzing **10** in the presence of hydrochloric acid (12 *M*). This new agent is currently being evaluated as a BNCT agent.

### 1.3.5 Synthesis of Compound B

We first planed to synthesize compound **B** by reaction of cyclopent-2-enone, **11,** with diethyl malonate as described in the scheme 1.3.3.[154] Michael addition reaction of diethyl malonate to **11** gave the desired compound **20** in good yields. The carbonyl group in **20** was protected as a ketal by treatment with ethylene glycol to yield **21.**[155] Intermediate diester **21** was converted to monoester **22** by basic hydrolysis with potassium hydroxide followed by thermal decarboxylation.[156] When compound **22** was subjected to reduction by $LiAlH_4$, we anticipated formation of alcohol **14.**[157,158] But, while purifying the reaction mixture via column chromatography, the ketal protected alcohol decomposed to give deprotected ketone **23**. Hence we decided to protect the ketone **20** using 1,2-hexanediol. While carrying out the Michael addition reaction of compound **11** with diethyl malonate, problems related to reproducibility arose, so we decided to synthesize the intermediate **14** using a different procedure, scheme 1.3.2. The Titanium catalyzed Sakurai reaction of cyclopent-2-enone, **11,** with allyltrimethylsilane generated **12** as a precursor to **13**.[159] We found that cyclopentanone ethanediol ketals are less stable during column chromatography compared to the corresponding 1,2 hexandiol derivatives which led us to prepare ketal **13**. Another advantage of using the 1,2-hexanediol derivative is intermediate 16 and 17 are less volatile. Ozonolysis of **13** followed by reduction of the corresponding ozonide by $LiAlH_4$ afforded alcohol **14** in quantitative yield. [160] Bromination of **14** using $CBr_4/PPh_3$ in dichloromethane at room temperature produced 3-bromoethylcyclopentanone acetal **15** in good yield.[151] The dehydrobromination of **15** to generate the alkenyl group was achieved using NaOH in PEG-600.[152] Deprotection of the

ketal group in, **16,** was achieved using dilute hydrochloric acid in refluxing ethanol, which gave the highly volatile ketone **17**. The reaction of crude ketone **17** with potassium cyanide and ammonium carbonate gave hydantoin **18**.[139] The hydroboration of **18** was accomplished using 3.0 equivalents of diisopinocampheylborane (Ipc2BH) in THF at room temperature. The resultant diisocampheylborane product was readily converted to boronic acid **19** by reaction with acetaldehyde and then aqueous HCl according to the literature procedure.[153] The hydrolysis of **19** in the presence of hydrochloric acid (12 *M*) produced **B** in good yield. This new agent is currently being is currently being evaluated as a BNCT agent.

### 1.3.6 Synthesis and Separation of Diastereoisomers of C.

1-Amino-3-boronocyclopentanecarboxylic, **C**, was synthesized starting from cyclopent-2-enone, **11**, as outlined in scheme 1.3.5. The first catalyst system tried for 1,4-diboration with **11** was copper(1) chloride and potassium acetate in dimethylformamide as solvent.[161,162] The reaction gave moderate yields. Changing reagent quantities as well as solvent did not improve the yields. A rhodium catalyst, chlorotris(triphenylphosphine)rhodium(I), was then examined but yields with the system were also poor.[163] GC analysis revealed numerous side products so this method was abandoned. We decided to treat **11** with copper(1) chloride and tributylphosphine in dimethylformamide; this system gave good yields of **24** (88 %).[164] It was noted that the reproducibility of this 1,4-addition reaction was heavily dependent on the activity of copper catalyst. To enhance the efficiency of the copper catalyst, a longer time period (~30 min) was used before the addition of the diboron reagent. Then **24** was treated with potassium cyanide and ammonium carbonate to give hydantoin **25** as a white solid.[139] Having obtained **25** as a solid, the next step was to separate the diastereoisomers of **25**. Attempts to separate the two diastereoisomers by column chromatography on alumina were unsuccessful due to the decomposition of the borate ester. Fortunately, we discovered that diastereoisomers, **26** and **27**, could be separated by recrystallization.

Various solvents were tried for the recrystallization in an attempt to separate diastereoisomers of **25**. In the initial studies, we found that recrystallization using methanol resulted in separation of diastereoisomers but the yields were moderate. Further investigation of recrystallization systems using a solvent system of chloroform-petroleum ether resulted in better separation of diastereoisomers. Finally chloroform-petroleum ether was chosen as best system for the separation of diastereoisomers to yield pure **26** and **27**. The X-ray crystal structure of compound **27** is shown in Fig. 1.3.3. We found that hydantoin **25** is formed in a 2:1 ratio of stereoisomers giving the *cis*-isomer as the major product. The hydrolysis of **26** and **27** in the presence of hydrochloric acid (12 *M*) produced boronated amino acids **28** and **29** in good yield.

### 1.3.7 Synthesis of Compound D

During the design of the synthesis of compound **D**, we found that it can be synthesized through titanium catalyzed Sakurai reaction of cyclopent-2-enone, **11**, with allyltrimethylsilane, as described in the synthesis of compound **B**.[159] The reaction of ketone **12** with potassium cyanide and ammonium carbonate gave hydantoin **30** in good yield. As outlined in scheme 1.3.5[139] the hydroboration of **30** was carried out using 3.0 equivalents of diisopinocampheylborane ($Ipc_2BH$) in THF at room temperature. The resultant diisocampheylborane product was readily converted to boronic acid **31** by reaction with acetaldehyde and then with aqueous HCl according to the literature procedure.[153] The hydrolysis of **31** in the presence of hydrochloric acid (12 *M*) produced **D** in good yield.

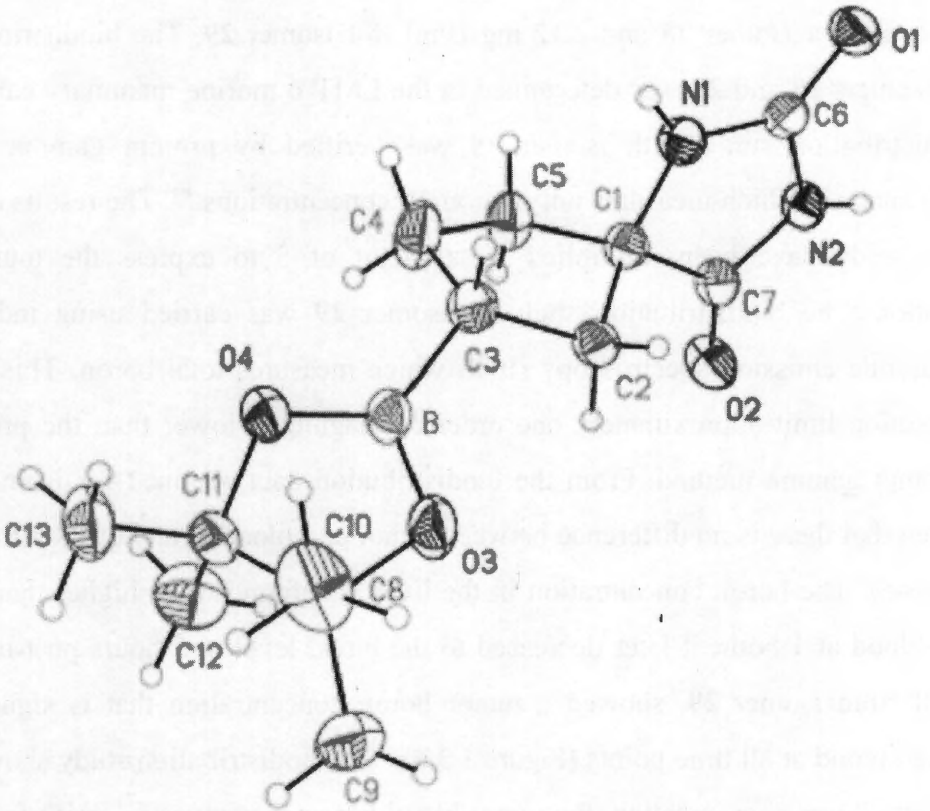



Fig 1.3.3 X- Ray crystal structure of compound **27**.

### 1.3.8 Results of Biodistrubution Studies of Diastereoisomers of 1-Amino-3-boronocyclopentanecarboxylic Acid, C.

To prepare injection solutions, amino acids (isomers **28** and **29**) were first solubilized as fructose complexes.[163] One millimole of **28** or **29** was combined with 1.1 millimoles of fructose in ~1 mL of water. In the injection solutions the boron concentration was kept at 1.87 mg B/mL for isomer **28** and 2.12 mg B/mL for isomer **29**. The biodistribution of diastereoisomers **28** and **29** was determined in the EMT-6 murine mammary carcinoma. The biodistribution study with isomer **28** was verified by prompt gamma neutron activation analysis which measures only boron-10 concentrations.[164] The results obtained from this study have been multiplied by a factor of 5 to express the total boron concentration. The biodistribution study of isomer **29** was carried using inductively coupled atomic emission spectroscopy (ICP) which measures total boron. This method has a detection limit approximately one order of magnitude lower than the previously noted prompt gamma method. From the biodistribution data obtained for isomer **28**, it can be seen that there is no difference between tumor and blood at any of the time points (Figure 1.3.5). The boron concentration in the liver was found to be higher than that in tumor or blood at 1 hour; it later decreased to the blood level at 5 hours post-injection. The result from isomer **29**, showed a tumor boron concentration that is significantly greater than blood at all time points (Figure 1.3.4). The biodistribution study showed that at 1, 3, and 5 hours post-injection, the tumor/blood boron concentration ratios for isomer **29** were found to be $2.8 \pm 0.8$, $2.4 \pm 0.6$, and $1.8 \pm 0.5$, respectively. It was observed that with isomer **29**, the normal tissues, skin, and brain were similar to blood at 1 hour. The boron concentration in the liver was higher than that in tumor at 1 hour. From this study it can be said that isomer **29** showed very promising tumor/normal tissue boron concentration ratios at 1 hour post-injection which is promising for BNCT. [165]

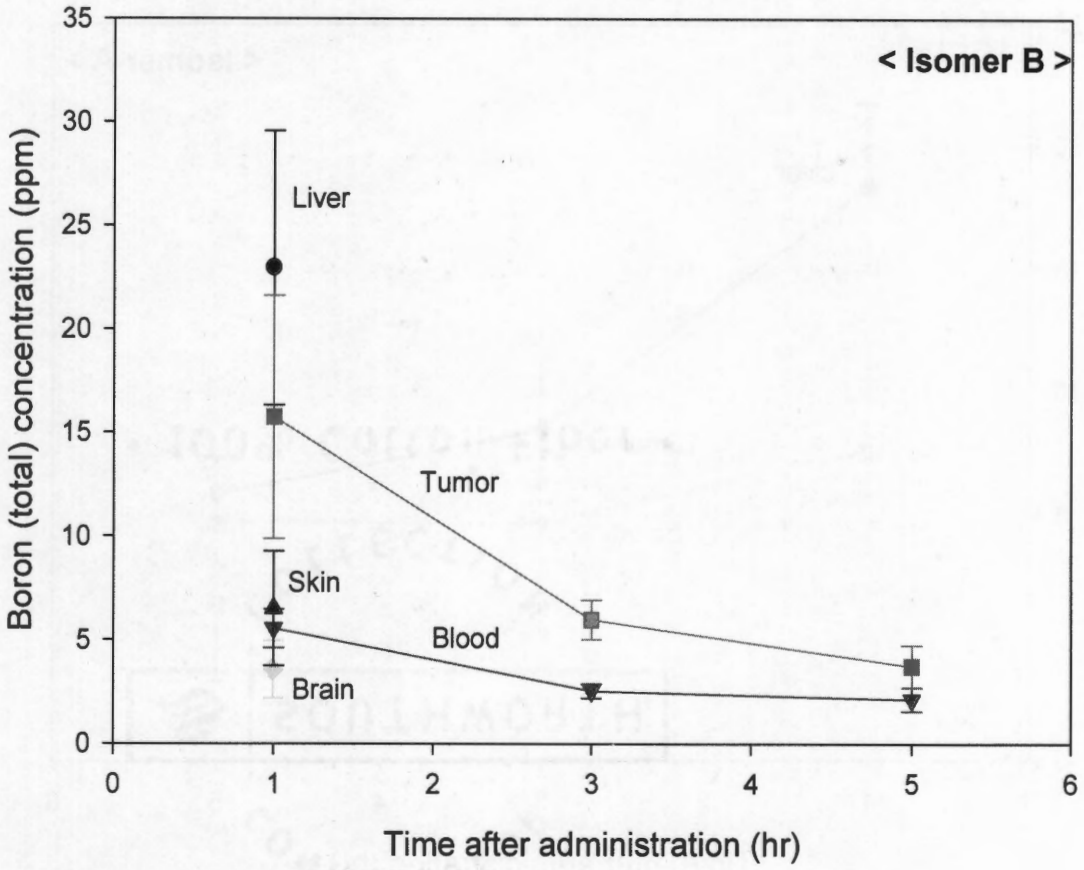



Fig. 1.3.4 Biodistribution of Compound **29**

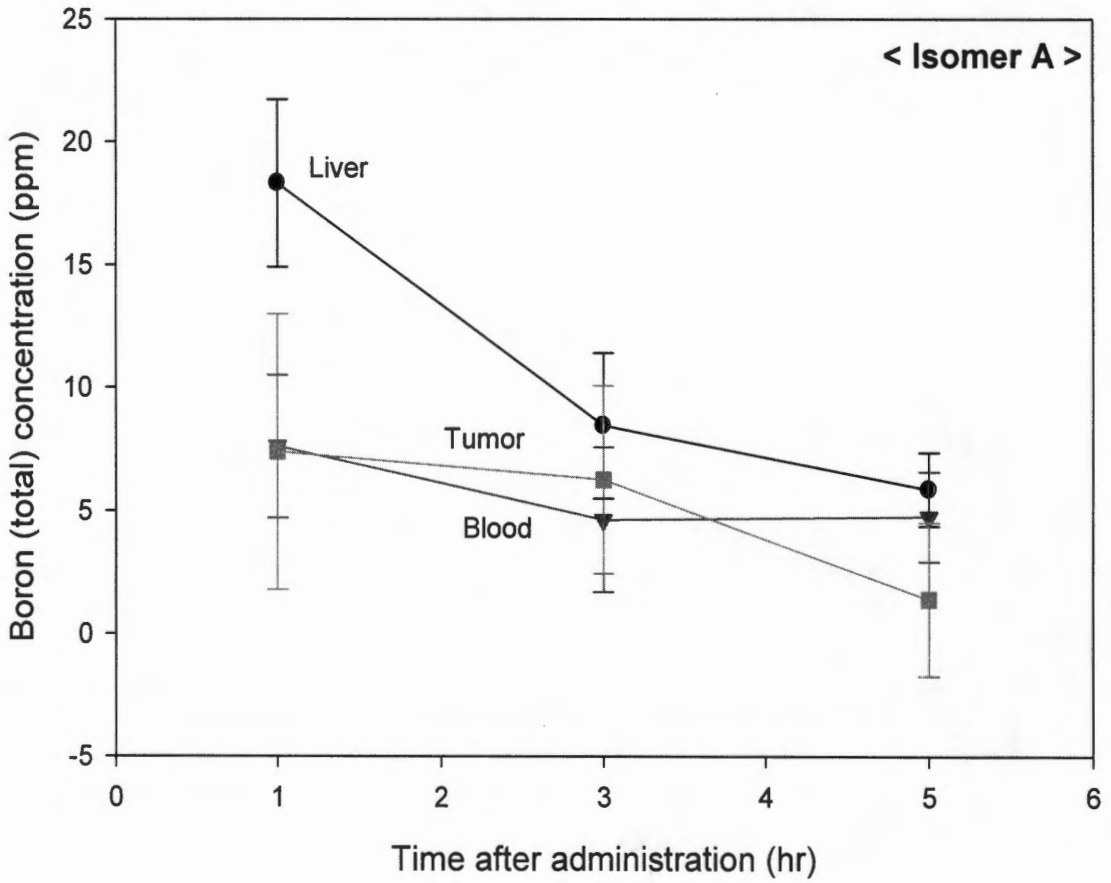
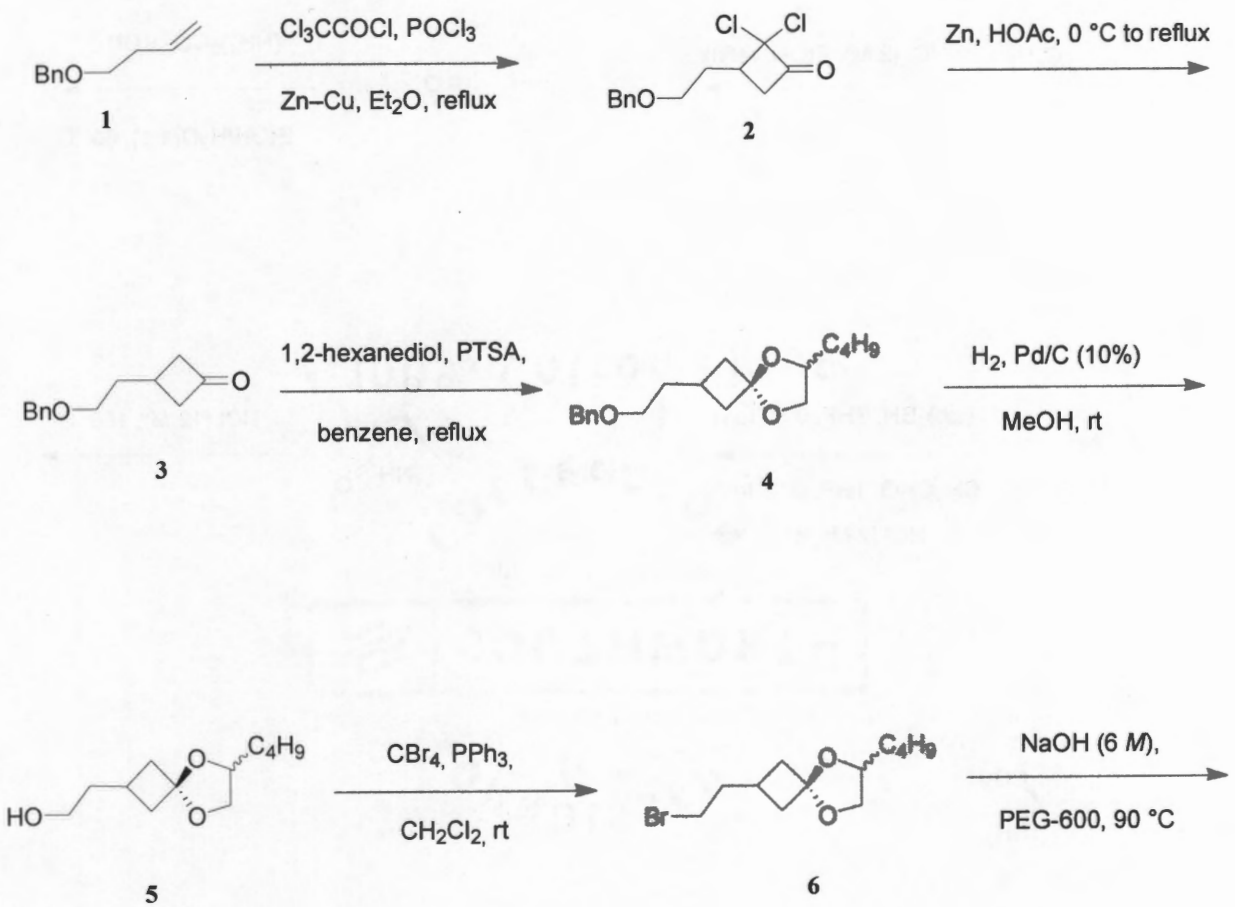
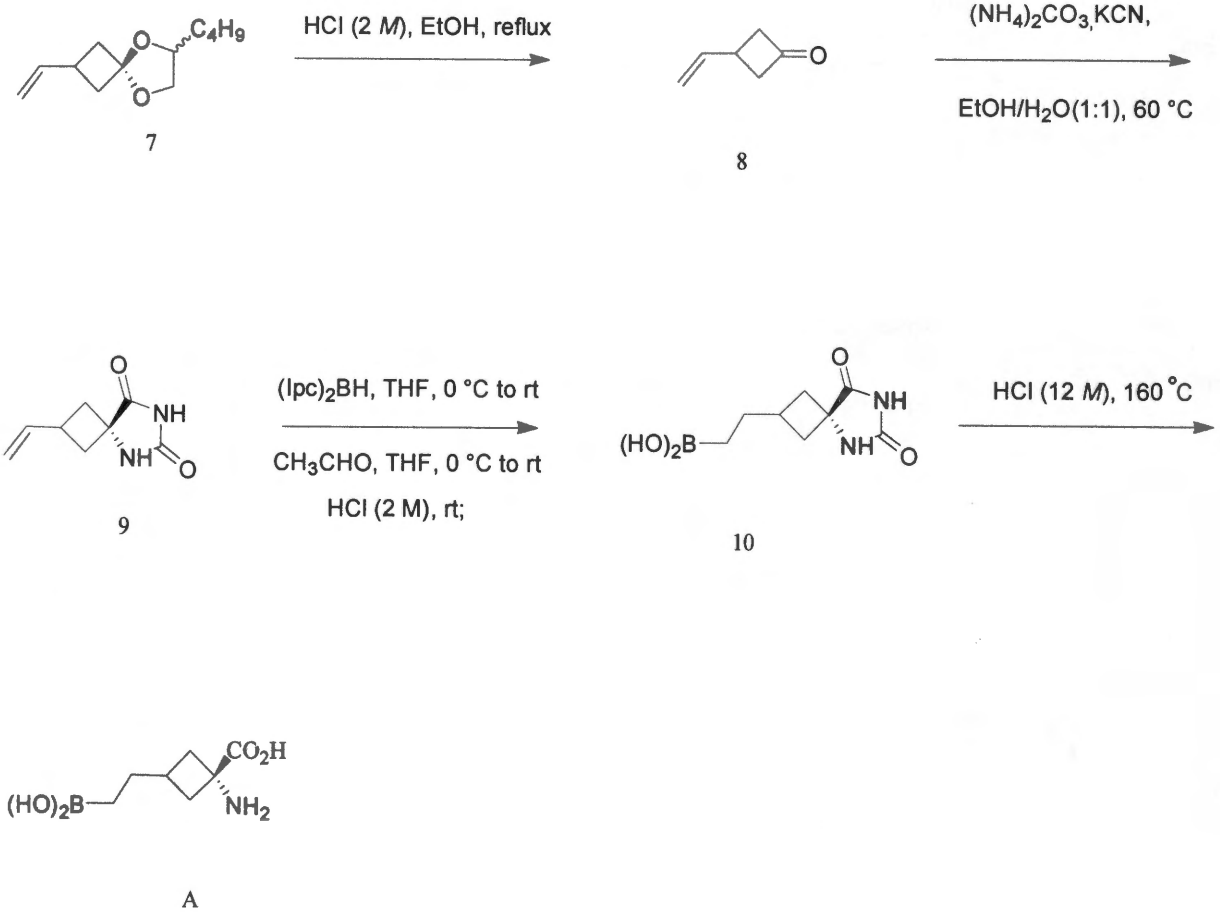



Fig. 1.3.5 Biodistribution of Compound **28**

**Scheme 1.3.1 Synthesis of compound A**

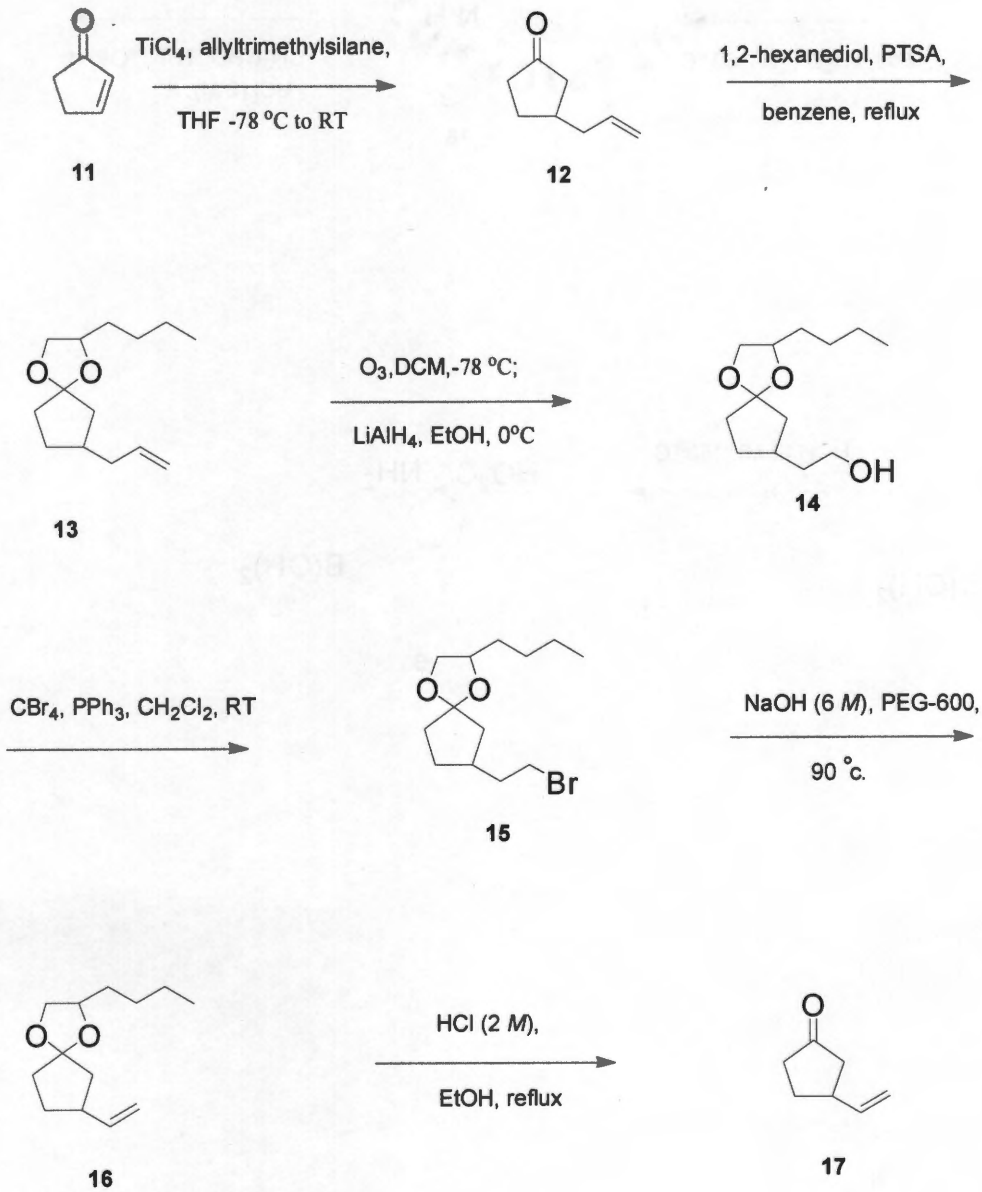


**Scheme 1.3.1 Synthesis of compound A**



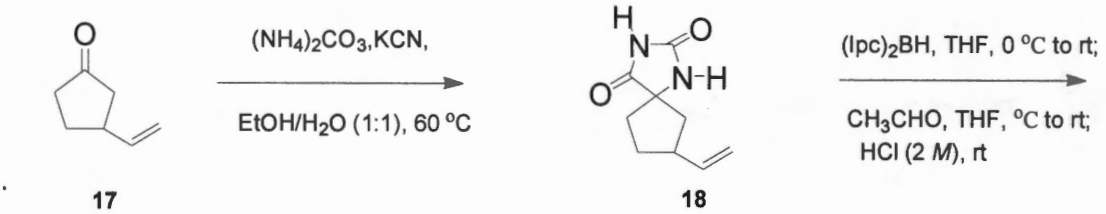

7 8 9 10 A

**Scheme 1.3.2 Synthesis of compound B**

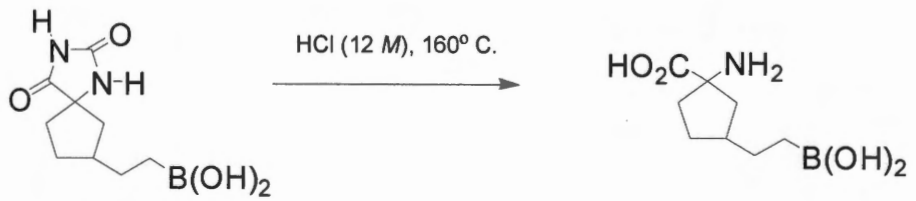



**11** **12** **13** **14** **15** **16** **17**

**Scheme 1.3.2 synthesis of compound B**

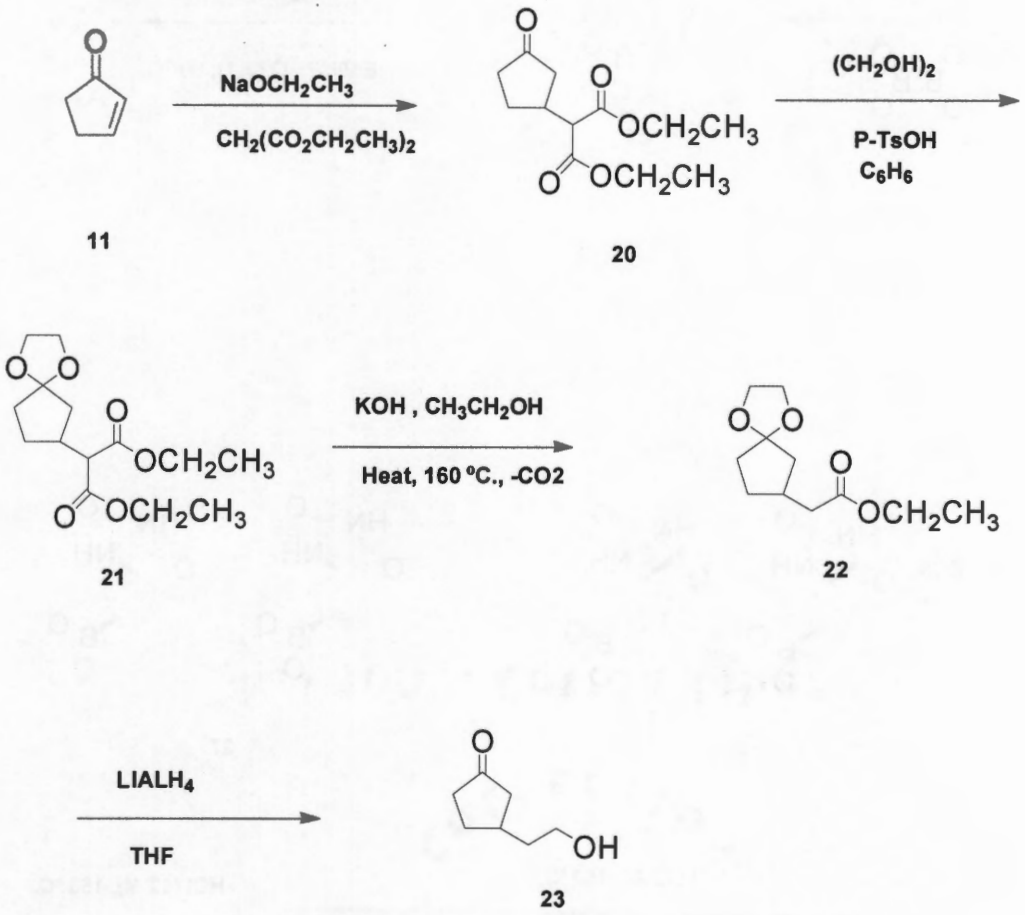



17 18



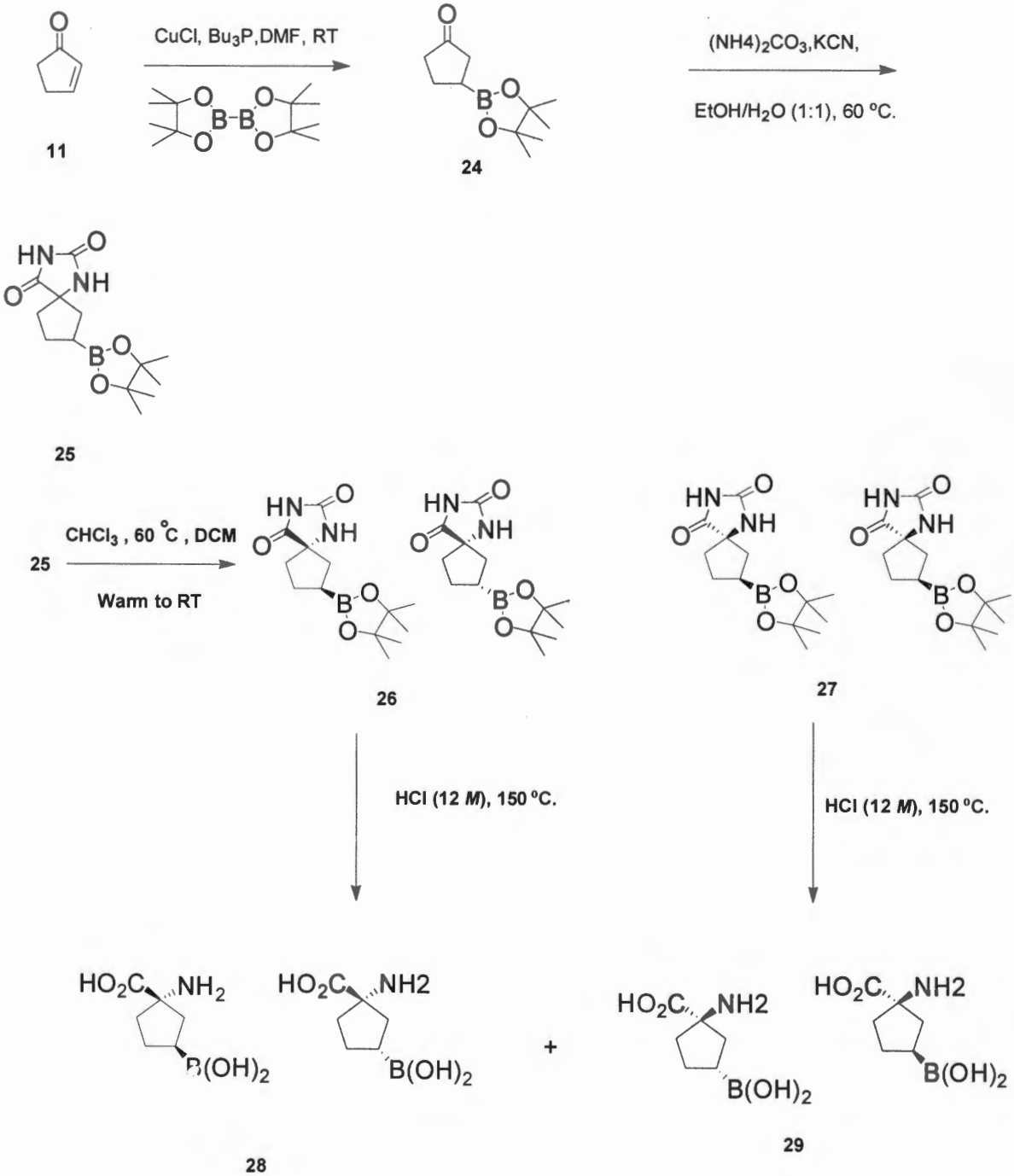

19 B

**Scheme 1.3.3 Alternate route to intermediate alcohol**

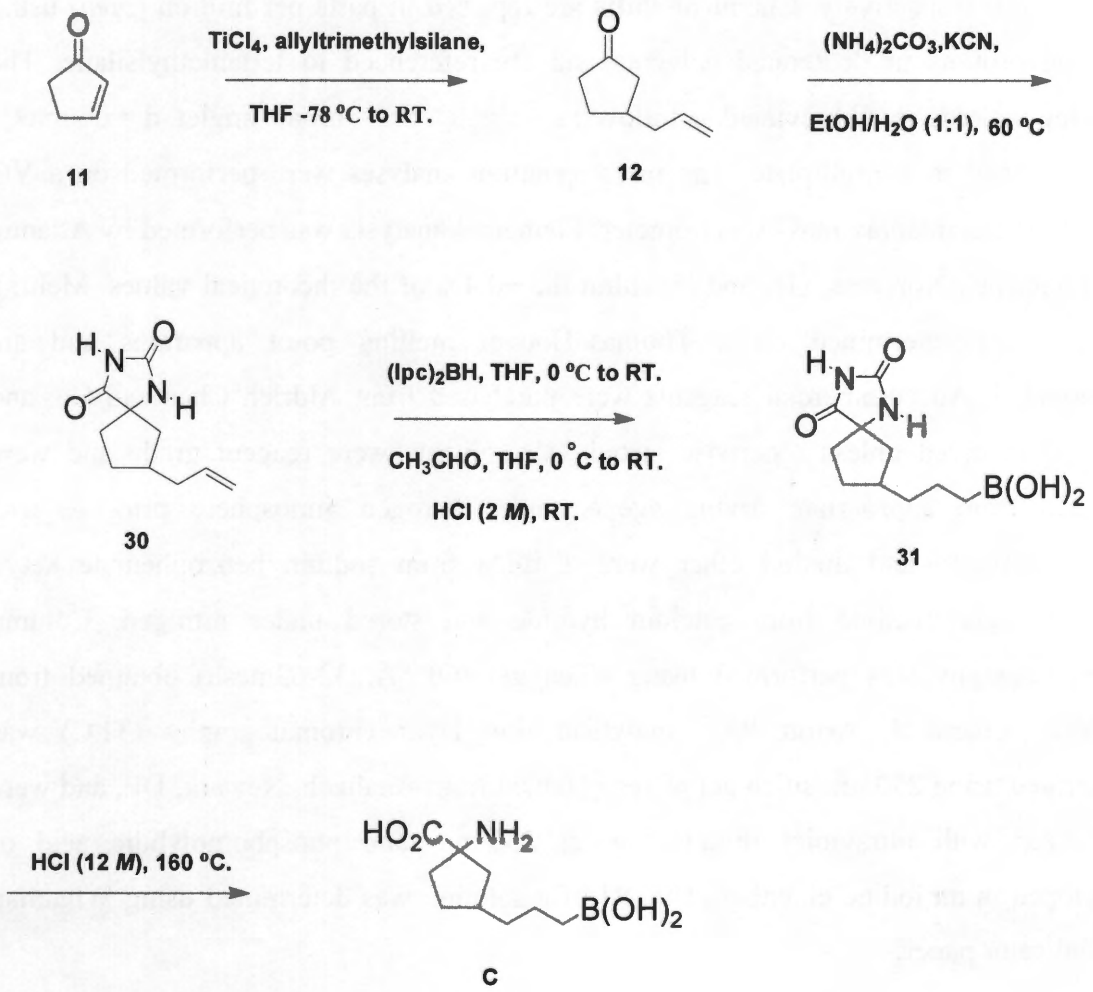



11 20 21 22 23

**Scheme 1.3.4 Synthesis and separation of diastereoisomers of Compound C**



**Scheme 1.3.5 Synthesis of compound D**



# CHAPTER 4 EXPERIMENTAL SECTION

## 1.4.1 General Methods

Proton ($^{1}H$) and carbon ($^{13}C$) nuclear magnetic resonance spectra were acquired either on a Bruker WP250 at 250.13 and 62.89 MHz or on a Varian Mercury 300 at 300.09 and 75.46 MHz, respectively. Chemical shifts are reported in parts per million (*ppm*) using residual protons in deuterated solvents and are referenced to tertamethylsilane. The splitting patterns are abbreviated as follows: s = singlet, brs = broad singlet, d = doublet, t = triplet, and m = multiplate. The mass spectrum analyses were performed on a VG Quattro II electrospray mass spectrometer. Elemental analysis was performed by Atlantic Microlab Inc., Norcross, GA and is within the ±0.4% of the theoretical values. Melting points were determined on a Thomas–Hoover melting point apparatus and are uncorrected. All commercial reagents were purchased from Aldrich Chemical Co. and used as received unless otherwise stated. All solvents were reagent grade and were distilled from appropriate drying agents under nitrogen atmosphere prior to use. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Benzene was distilled from calcium hydride and stored under nitrogen. Column chromatography was performed using silica gel (60 °A, 32-63mesh) obtained from Bodman Chemical, Aston PA. Analytical thin layer chromatography (TLC) was performed using 250 μm silica gel plates obtained from Analtech, Newark, DE, and were visualized with ultraviolet illumination at 254 nm and phosphomolybdic acid or developed in an iodine chamber. The pH of a solution was determined using Whatman pH indicator paper.

All glassware, syringes, and needles were dried in an oven and cooled under nitrogen prior to use.

### 1.4.2 Experimental procedure for unnatural cyclic amino acid Acids, A.

#### 1.4.2.1 Synthesis of Benzyloxyethyl-2,2-dichlorocyclobutanone, 2.

A 250 mL three-necked, round-bottomed flask, equipped with an addition funnel and reflux condenser, was charged with but-3-enyloxymethylbenzene (30 mmol, 4.86 g), freshly prepared zinc copper couple (100 mmol, 6.5 g), and anhydrous diethyl ether (50 mL). A solution of trichloroacetyl chloride (60 mmol, 6.7 mL) and phosphorus oxychloride (60 mmol, 5.6 mL) in diethyl ether (100 mL) was placed in the addition funnel and the solution added dropwise over a period of 30 min. After the addition was complete, the mixture was refluxed at 55 °C (oil bath) for 2 days under an argon atmosphere, cooled to room temperature, and filtered through a pad of Celite. Additional diethyl ether was used to wash the Celite. The solvent from the combined filtrates was removed *in vacuo* and the residue dissolved in petroleum ether (3x100 mL). The clear solution was decanted into a separatory funnel, washed with water (2x50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate, and concentrated with a rotary evaporator to obtain **2** as a light yellow liquid. Compound **2** was unstable on silica gel and was therefore used directly for the next step.

#### 1.4.2.2 Synthesis of 3 -(Benzyloxyethyl)cyclobutanone, 3.

Crude **2** was dissolved in glacial acetic acid (20 mL) and zinc dust (10 g, excess) was added in portions. The mixture was stirred at room temperature for 30 min and then heated at 120 °C (oil bath) for 12 h. Thin-layer chromatography indicated the disappearance of the starting material. The mixture was cooled to room temperature,

neutralized with saturated aqueous sodium bicarbonate at 0 °C, and passed through a pad of Celite. Ethyl acetate was used to wash the Celite. The combined filtrate was then extracted with ethyl acetate (3x50 mL). The combined organic layer was washed with water (2x20 mL) and brine (20 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to obtain **3** as a thick light yellow liquid. The crude product was purified by column chromatography (EtOAc: hexanes = 1:15). 3-(2-Benzyloxyethyl)cyclobutanone, **3**, was obtained as a colorless liquid 3.3 g (56%) based on allyl benzyl ether). $^{1}$H NMR (250 MHz, $CDCl_3$) δ 7.25–7.34 (m, 5H), 4.50 (s, 2H), 3.58–3.49 (m, 2H), 3.08–3.19 (m, 2H), 2.82–2.54 (m, 3H), 2.07–1.86 (m, 2H); $^{13}$C NMR (63 MHz, $CDCl_3$) δ 208.1, 138.0, 128.3, 127.6, 72.9, 68.8, 52.5, 36.0, 21.3. Anal. Calcd for $C_{13}H_{16}O_2$: theory C, 76.44; H, 7.90; Found: C, 76.77; H 7.91.

### 1.4.2.3 Synthesis of 3-(Benzyloxyethyl)cyclobutanone Ketal, 4.

A 250 mL round-bottomed flask equipped with a Dean-Stark apparatus and a reflux condenser was charged with **3** (8.16 g, 40 mmol), hexane-1,2-diol (6.2 g, 44 mmol), and *p*-toluenesulfonic acid (500 mg) in benzene (150 mL). The mixture was refluxed at 120 °C (oil bath) for 14 h and the progress of the reaction was monitored by TLC. After 14 h the flask was cooled to room temperature and saturated aqueous $NaHCO_3$ (20 mL) was added. The mixture was transferred to a separatory funnel, washed with $H_2O$ (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a colorless oil. The product was purified by column chromatography (EtOAc:hexanes = 1:20) to yield 11.2 g (89%) of **4** as a colorless liquid. $^{1}$H NMR (250 MHz, $CDCl_3$) δ 7.24–7.32 (m, 5H), 4.46 (s, 2H), 3.92–3.98 (m, 2H), 3.39–3.44 (d, $J$ = 6.26 Hz, 3H), 2.36–2.44 (dd, $J$ = 12.3, 6.7 Hz, 3H), 1.61–2.06 (m, 4H), 1.48–1.32 (m, 6H), 0.92–0.67 (m, 3H), $^{13}$C NMR (63 MHz, $CDCl_3$) δ 138.4, 128.1, 127.3, 106.7, 106.8, 76.4, 75.8, 72.72, 68.9, 68.7, 41.7, 41.4, 38.2, 33.3, 33.9, 27.7, 22.5, 13.9. Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.74; H, 9.30.

### 1.4.2.4 Synthesis of 3-(Hydroxyethyl)cyclobutynone Ketal, 5.

To a 100 mL round-bottomed flask fitted with a septum cap were added compound **4** (11.7 g, 38.6 mmol), 10% Pd/C (1.12 g), and MeOH (60 mL). The air in the flask was removed under vacuum and $H_2$ was introduced by using a $H_2$-filled balloon. After being stirred for 24 h at room temperature, the mixture was filtered and the residual Pd/C was washed with MeOH. Concentration of the filtrate and washings under reduced pressure yielded 7.9 g (97%) of the colorless product **5**. $^1$H NMR (250 MHz, $CDCl_3$) δ 3.94–3.99 (m, 2H), 3.40–3.57 (m, 2H), 3.07 (s, 1H), 2.38–2.44 (m, 2H), 1.78–2.07 (m, 3H), 1.72–1.67 (m, 2H), 1.25–1.38 (m, 6H), 0.87 (t, $J$ = 6.48 Hz, 3H); $^{13}$C NMR (63 MHz, $CDCl_3$) δ 106.8, 106.8, 75.9, 75.3, 68.9, 68.4, 66.5, 60.9, 41.5, 40.6, 39.0, 37.2, 33.2, 32.8, 27.7, 22.5, 21.6, 13.8. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 66.24; H, 10.41.

### 1.4.2.5 Synthesis of 3-(Bromomethyl)cyclobutanone Ketal, 6.

To a 250 mL round-bottomed flask fitted with a septum cap were added compound **5** (6.42 g, 30.0 mmol), $CBr_4$ (12.5 g, 37.5 mmol), and $CH_2Cl_2$ (50 mL). The solution was cooled in an ice-water bath. Then $Ph_3P$ (11.8 g, 45.0 mmol) in $CH_2Cl_2$ (70 mL) was added dropwise via syringe. After addition was complete, the bath was removed and the mixture stirred for an additional 6 h. The solvent was removed under reduced pressure and the residue extracted into ether (5x40 mL). The ether layer was concentrated in vacuo and the residue purified by column chromatography (EtOAc:hexanes = 1:30) to yield 7.6 g (91%) of **6** as a colorless liquid. $^1$H NMR (250 MHz, $CDCl_3$) δ 3.93–4.06 (m, 2H), 3.49 (d, $J$ = 7.02 Hz, 2H), 3.42–3.48 (m, 1H), 2.42–2.54 (m, 3H), 2.03–2.15 (m, 2H), 1.16–1.58 (m, 6H), 0.91 (t, $J$ = 6.78 Hz, 3H); $^{13}$C NMR (63 MHz, $CDCl_3$) δ 105.4, 105.2, 76.0, 75.8, 69.1, 68.8, 41.2, 41.1, 40.9, 38.4, 33.2, 33.0, 27.8, 27.7, 27.6, 22.6, 13.9. Anal. Calcd for $C_{12}H_{21}O_2Br$: C, 51.99; H, 7. 64. Found: C, 51.96; H, 7.72.

### 1.4.2.6 Synthesis of 3-Vinylcyclobutanone Ketal, 7.

A 100 mL round-bottomed flask equipped with a reflux condenser was charged with **5** (6.9 g, 25 mmol), PEG-600 (1.5 g), 50% aqueous NaOH solution (15 mL), and benzene (20 mL). The mixture was refluxed at 90 °C (oil bath) and the progress of the reaction was monitored by TLC. After 16 h, the flask was cooled to room temperature and water (20 mL) added. The mixture was transferred to a separatory funnel, the product extracted with ether (3x20 mL), and the combined ether layer washed with $H_2O$ (2x15 mL) and then brine (15 mL). After the solution was dried over anhydrous MgSO4, the solvent was removed by distillation (**Caution**: compound **7** is volatile). The product was purified by column chromatography ($Et_2O$: hexanes = 1:20) to afford **7** as a colorless liquid 3.1 g (63%). $^1$H NMR (250 MHz, $CDCl_3$) δ 5.88–5.98 (m, 2H), 4.92–5.02 (m, 2H), 3.95–4.02 (m, 2H), 3.43–3.52 (m, 1H), 2.42–2.51 (m, 2H), 2.17–2.37 (m, 2H), 1.81–1.84 (m, 6H), 0.85 (t, $J$ = 6.33 Hz, 3H); $^{13}$C NMR (63 MHz, $CDCl_3$) δ 142.07, 113.12, 106.17, 75.6, 75.3, 69.2, 68.6, 41.9, 33.4, 32.9, 28.5, 27.8, 22.8, 14.0. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.35; H, 10.27.

### 1.4.2.7 Synthesis of 3-Vinylcyclobutanone, 8.

A 100 mL round-bottomed flask was charged with compound **7** (588 mg, 3.0 mmol) dissolved in a mixture of ethanol (10 mL) and aqueous hydrochloric acid (4 mL, 2.0 *M*). The mixture was refluxed overnight at which time TLC indicated complete disappearance of the starting ketal. After cooling to room temperature, the mixture was extracted with ether (3x20 mL), the combined organic phases dried over anhydrous $MgSO_4$, and the solvent removed by distillation (**Caution**: compound **8** is volatile). Compound **8** was used directly for the next step.

### 1.4.2.8 Synthesis of Hydantoin of 3-Vinylcyclobutanone, 9.

A 50 mL Ace pressure tube was charged with ketone **8** (1.44 g, 15 mmol), aqueous ethanol (50%, 20 mL), potassium cyanide (2.0 g, 30 mmol), and ammonium carbonate (7.2 g, 75 mmol). The reaction vessel was sealed and heated at 60 °C (oil bath) for 8 h. A light yellow precipitate formed. The mixture was cooled to room temperature and the vessel carefully opened in a fume hood. The mixture was concentrated under reduced pressure and the solid obtained was purified by column chromatography (EtOAc: hexanes = 2:1) to afford 1.79 g (71%) of **9** as a white solid. $^{1}$H NMR (250 MHz, $CD_3OD$) δ 9.96 (s, 1H), 8.26 (s, 1H ), 5.60–5.94 (m, 1H), 4.94–5.05 (m, 2H), 2.94–2.97 (m, 1H), 2.19–2.21 (m, 2H); $^{13}$C NMR (63 MHz, $CDCl_3$) (DMSO–$d_6$) δ 178.8, 155.9, 141.5, 114.08, 57.4, 40.50, 37.09, 29.4. Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 56.54; H, 6.12; N, 16.35.

### 1.4.2.9 Synthesis of Boronohydantoin, 10.[154]

Diisopinocampheylborane, $(Ipc)_2BH$, was prepared according to the literature procedure.[167] A 100 mL round-bottomed flask was fitted with a septum and a magnetic stirring bar and connected to a nitrogen bubbler. The flask was flushed with nitrogen and held at a positive static pressure of nitrogen. Borane-THF (50 mmol, 50 mL, 1.0 *M*) was added to the flask, which was cooled to 0 °C, then (*R*)-pinene (18.4 mL, 115 mmol) was added slowly and the mixture stirred at 0 °C for 1 h. The reaction was maintained at 0 °C for 3 days to give the required crystalline product. Compound **9** (415 mg, 2.5 mmol) was placed in a 150 mL round-bottomed flask and dissolved in THF (10 mL) at 0 °C. $(Ipc)_2BH$ (7.5 mmol) in THF (10 mL) was added dropwise via a syringe. The mixture was allowed to warm to room temperature and stirred for 16 h. Freshly distilled acetaldehyde (12 mmol) was added and the mixture was stirred for an additional 12 h. Excess acetaldehyde was removed under vacuum and the mixture was hydrolyzed with aqueous hydrochloric acid (5 mL, 2.0 *M*). The mixture was extracted with EtOAc (3x30 mL) and the combined organic phase dried over anhydrous $MgSO_4$. The solvent was

removed under reduced pressure and the residue purified by column chromatography (methanol) to afford **10** as a white solid 323 mg (61%). $^1$H NMR (DMSO-$d_6$) δ 10.0 (s, 1H), 8.16 (s, 1H), 2.18–2.26 (m, 2H), 1.89–1.19 (m, 1H), 1.42–1.44 (m, 2H), 1.17–1.18 (m, 2H), 0.48–0.50 (m, 2H); $^{13}$C NMR (63 MHz, $CDCl_3$) δ 178.9, 155.9, 57.4, 40.5, 38.0, 38.7, 28.7.

### 1.4.2.10 1-Amino-3-[(dihydroxyboryl)ethyl]cyclobutanecarboxylic acid, A.

Boronohydantoin **10** (318 mg, 1.5 mmol) was placed in a 25-mL Ace pressure tube along with hydrochloric acid (4 mL, 12 *M*). The tube was sealed and heated to 150 °C (oil bath) for 40 h. It was then cooled to room temperature and carefully opened (Hood!), charcoal was added, and the resulting mixture was filtered through a pad of Celite. The Celite pad was washed with water. Removal of the water under reduced pressure gave a white solid 226 mg (81%). $^1$H NMR ($D_2O$) δ 2.17–2.64 (m, 4H), 1.93–2.08 (m, 1H), 1.37–1.53 (m, 2H), 0.53–0.62 (m, 2H); $^{13}$C NMR (63 MHz, $CDCl_3$) δ 177.5, 57.1, 39.2, 34.3, 33.4, 33.1, 14.7. HR-FAB-MS (M + H + gly - $2H_2O$); obtained in a glycerol matrix) calcd for $C_{10}H_{19}BNO_5$ 244.1358; Found: 244.1369.

## 1.4.3 Experimental Procedure for Unnatural Cyclic Amino Acid, B

### 1.4.3.1 Synthesis of 3-Allylcyclopentanone,12.

To a l00-mL three-necked, round-bottomed flask was fitted a pressure-equalizing dropping funnel and a reflux condenser attached to a nitrogen inlet. In the flask were placed (4.0 g, 0 40 mol) of cyclopentenone and 30 mL of dry methylene chloride. The flask was immersed in a dry ice-acetone bath. Titanium chloride (48 mL, 0.40 mmol) was

slowly added via syringe to the stirred mixture. The solution turned yellow at this time. After 5 min, a solution of 10.9 g (96 mmol) of allyltrimethylsilane in 30 mL of dry methylene chloride was added dropwise with stirring over a 10-min period. The resulting red-violet reaction mixture was stirred for 2 h at -78 °C. Then, it was hydrolyzed by addition of 40 mL of water and, after the addition of 40 mL of ethyl ether with stirring, allowed to warm to room temperature. The organic layer and the ether extracts were combined and washed successively with 30 mL of saturated $NaHCO_3$ and 30 mL of brine, dried over anhydrous $Na_2SO_4$, and the solvent evaporated at reduced pressure. Bulb-to-bulb distillation using a Kugelrohr apparatus produced 5.8g (96%) of **12**. $^1H$ NMR (250 MHz, $CDCl_3$) δ 5.74–5.81 (dd, $J$ = 7.2 Hz,1H), 5.02–5.09 (dd, $J$ = 16.0 Hz, 2H), 2.07–2.32 (m, 7H), 1.80–1.90 (dd, $J$ = 9.2 Hz, 1H), 1.53–1.60 (m, 1H); $^{13}C$ NMR (63 MHz, $CDCl_3$) δ 219.3, 136.1, 116.3, 44.6, 39.4, 38.2, 38.5, 28.9.

### 1.4.3.2 Synthesis of 3-Allylcyclopentanone Ketal, 13.

A 250 mL round-bottomed flask equipped with a Dean-Stark apparatus and a reflux condenser was charged with **12** (4.96 g, 40 mmol), hexane-1,2-diol (6.2 g, 44 mmol), and *p*-toluenesulfonic acid (500 mg) in benzene (150 mL). The mixture was refluxed at 120 °C (oil bath) for 14 h and the progress of the reaction was monitored by TLC. After 14 h, the flask was cooled to room temperature and saturated aqueous $NaHCO_3$ (20 mL) was added. The mixture was transferred to a separatory funnel, washed with $H_2O$ (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a colorless oil. The product was purified by column chromatography (EtOAc: hexanes = 1:20) to yield 8.78 g (97%) of **13** as a colorless liquid. $^1H$ NMR (250 MHz, $CDCl_3$) δ 5.68–5.82 (dd, $J$ = 7.2 Hz, 1H), 4.93–5.04 (dd, $J$ = 16.0 Hz, 2H), 3.92 (m, 2H), 3.38 (m, 1H), 1.25–2.27 (m, 15H), 0.85 (dd, $J$ = 7.2 Hz, 3H); $^{13}C$ NMR (63 MHz, $CDCl_3$) δ 137.4,

117.9, 115.2, 76.01, 69.3, 43.1, 40.0, 37.1, 36.4, 33.2, 29.9, 27.8, 22.8, 13.9. Anal. Calcd. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.65; H, 10.76.

### 1.4.3.3 Synthesis of 3-(2Hydroxyethyl)cyclopentanone Ketal,14.

To a 250 mL round-bottomed flask compound **13** (25 mmol, 4.48 g) was dissolved in 30 mL. $CH_2Cl_2$ was added and ozone passed through the solution at -78 °C for the necessary time (as determined by potassium iodide assay). The solution was concentrated under reduced pressure to evaporate the $CH_2Cl_2$. Then the ozonide was dissolved into 40 mL of diethyl ether and was decomposed at 0 °C by slowly adding (20mmol, 74mg) of lithium aluminum hydride with stirring and adequately protected from atmospheric moisture. The reaction mixture was then further decomposed by addition of water (5 mL) followed by 45 mL of 15% aqueous sulfuric acid. Product **14** was obtained in 3.54 g (62%) yield by ether extraction, and removal of solvent under reduced pressure as a colorless liquid. $^1$H NMR (250 MHz, $CDCl_3$) δ 3.95–4.02 (dd, $J$ = 7.5, 2H), 3.61–3.66 (dd, $J$ = 12.5, 2H), 3.42 (m, 1H), 1.28–2.09 (m, 15H), 0.67 (dd, $J$ = 7.2, 3H); $^{13}$C NMR (63 MHz, $CDCl_3$) δ 117.6, 75.9, 72.2, 69.2, 61.6, 43.3, 38.8, 36.4, 34.2, 30.3, 27.6, 22.6, 13.9. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68 38; H, 10.59. Found: C, 68.02; H, 10.74.

### 1.4.3.4 Synthesis of 3-(2-Bromoethyl)cyclopentanone Ketal, 15.

To a 250 mL round-bottomed flask fitted with a septum cap were added compound **14** (6.84 g, 30.0 mmol), $CBr_4$ (12.5 g, 37.5 mmol), and $CH_2C1_2$ (50 mL). The solution was cooled in an ice-water bath. Then, $Ph_3P$ (11.8 g, 45.0 mmol) in $CH_2C1_2$ (70 mL) was added dropwise via syringe. After addition was complete, the bath was removed and the mixture stirred for an additional 6 h. The solvent was removed under reduced pressure and the residue extracted into ether (5x40 mL). The ether layer was concentrated *in vacuo* and the residue purified by column chromatography (EtOAc:hexanes = 1:30) to yield

7.83 g (90%) of **15** as a colorless liquid. $^{1}$H NMR (250 MHz, $CDCl_3$) δ 3.47–4.01 (m, 2H), 3.30–3.49 (m, 3H), 1.25–2.12 (m, 15H), 0.87 (dd, $J$ = 7.2, 3H); $^{13}$C NMR (63 MHz, $CDCl_3$) δ 117.5, 76.9, 69.2, 40.6, 38.8, 38.3, 35.9, 33.0, 31.9, 29.7, 27.6, 22.6, 13.9. Anal. Calcd for $C_{13}H_{23}O_2Br$: C, 53.61; H, 7.96. Found: C, 53.91; H, 8.01.

### 1.4.3.5 Synthesis of 3-VinylcyclopentanoneKetal, 16.

A 100 mL round-bottomed flask equipped with a reflux condenser was charged with **15** (7.25 g, 25 mmol), PEG-600 (1.5 g), 50% aqueous NaOH solution (15 mL), and benzene (20 mL). The mixture was refluxed at 90 °C (oil bath) and the progress of the reaction was monitored by TLC. After 16 h, the flask was cooled to room temperature and water (20 mL) added. The mixture was transferred to a separatory funnel, the product extracted with ether (3x20 mL), and the combined ether layer washed with $H_2O$ (2x15 mL) and then brine (15 mL). After the solution was dried over anhydrous $MgSO_4$, the solvent was removed by distillation (**Caution**: compound **16** is volatile). The product was purified by column chromatography (Et2O: hexanes = 1:20) to afford **16** as a colorless liquid 3.4 g (66%). $^{1}$H NMR (250 MHz, $CDCl_3$) δ 5.65–5.79 (m, 1H), 4.81–4.99 (m. 2H), 3.86–3.98 (m, 2H), 3.36–3.45 (m, 1H), 2.55–2.56 (m, 1H), 1.20–1.98 (m, 12H), 0.76 (dd, $J$ = 12.5, 3H); $^{13}$C NMR (63 MHz, $CDCl_3$) δ 142.1, 117.8, 113.0, 76.5, 68.3, 61.2, 41.9, 38.7, 33.2, 31.6, 27.9, 22.7, 14.1.

### 1.4.3.6 Synthesis of 3-Vinylcyclopentanone, 17.

A 100 mL round-bottomed flask was charged with compound **16** (1.1g, 5.0 mmol) dissolved in a mixture of ethanol (10 mL) and aqueous hydrochloric acid (9 mL, 2.0 *M*). The mixture was refluxed overnight at which time TLC indicated complete disappearance of the starting ketal. After cooling to room temperature, the mixture was extracted with

ether (3x20 mL), the combined organic phases dried over anhydrous MgSO4, and the solvent removed by distillation (**Caution**: compound **17** is volatile). Due to volatile nature of **17**, it was directly used in the next step.

### 1.4.3.7 Synthesis of Hydantoin of 3-Vinylcyclopentanone, 18.

A 50 mL Ace pressure tube was charged with ketone **17** (1.65g, 15 mmol), aqueous ethanol (50%, 20 mL), potassium cyanide (2.0 g, 30 mmol), and ammonium carbonate (7.2 g, 75 mmol). The reaction vessel was sealed and heated at 60 °C (oil bath) for 8 h. A light yellow precipitate formed. The mixture was cooled to room temperature and the vessel carefully opened in a fume hood. The mixture was concentrated under reduced pressure and the solid obtained was purified by column chromatography (EtOAc:hexanes = 2:1) to afford 1.83 g (67%) of **18** as a white solid. $^{1}$H NMR (250 MHz, $CD_3OD$) δ 9.88 (s, 1H), 8.25 (s, 1H), 5.75–5.88 (m, 1H), 4.90–5.05 (m, 2 H), 1.45–2.48 (m, 7H); $^{13}$C NMR (63 MHz, $CDCl_3$) δ 179.4, 156.1, 141.2, 113.8, 67.6, 43.4, 42.7, 38.5, 31.2. Anal. Calcd for $C_9H_{12}O_2N_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.71; H, 6.72; N, 15.33.

### 1.4.3.8 Synthesis of Boronohydantoin, 19.

Diisopinocampheylborane, $(Ipc)_2BH$, was prepared according to the literature procedure.[186] A 100 mL round-bottomed flask was fitted with a septum and a magnetic stirring bar and connected to a nitrogen bubbler. The flask was flushed with nitrogen and held at a positive static pressure of nitrogen. Borane-THF (50 mmol, 50 mL, 1.0 *M*) was added to the flask, which was cooled to 0 °C, then (*R*)-pinene (18.4 mL, 115 mmol) was added slowly and the mixture stirred at 0 °C for 1 h. The reaction was maintained at 0 °C for 3 days to give the required crystalline product. Compound **18** (450 mg, 2.5 mmol) was placed in a 150 mL round-bottomed flask and dissolved in THF (10 mL) at 0 °C. $(Ipc)_2BH$ (7.5 mmol) in THF (10 mL) was added dropwise via a syringe. The mixture was allowed to warm to room temperature and stirred for 16 h. Freshly distilled

acetaldehyde (12 mmol) was added and the mixture was stirred for an additional 12 h. Excess acetaldehyde was removed under vacuum and the mixture was hydrolyzed with aqueous hydrochloric acid (5 mL, 2.0 *M*). The mixture was extracted with EtOAc (3x30 mL) and the combined organic phase dried over anhydrous MgSO4. The solvent was removed under reduced pressure and the residue purified by column chromatography (methanol) to afford **19** as a white solid 384 mg (68%). $^{1}$H NMR (DMSO-$d_6$) δ 10.5 (s, 1H), 8.05 (s, 1H), 1.15–1.97 (m, 9H), 0.54 (t, $J$ = 12.4 Hz, 2H); $^{13}$C NMR (63 MHz, $CDCl_3$) δ 187.4, 179.2, 156.2, 68.3, 59.7, 43.9, 36.1, 29.9, 20.7. HR-FAB-MS (M + H + gly - $2H_2O$; obtained in a glycerol matrix) calcd for $C_{12}H_{19}BN_2O_5$: 283.1475; Found: 183.1472.

### 1.4.3.9 Synthesis of 1-Amino-3-[(dihydroxyboryl)ethyl]cyclopentanecarboxylic acid, B.

Boronohydantoin **19** (339 mg, 1.5 mmol) was placed in a 25 mL Ace pressure tube along with hydrochloric acid (4 mL, 12 *M*). The tube was sealed and heated to 150 °C (oil bath) for 40 h. It was then cooled to room temperature, carefully opened (Hood!), charcoal added, and the resulting mixture filtered through a pad of Celite. The Celite pad was washed with water. Removal of the water under reduced pressure gave a white solid 244 mg (81%). $^{1}$H NMR ($D_2O$) δ 0.62–0.83 (m, 2H), 1.02–1.89 (m, 9H); $^{13}$C NMR (63 MHz, $CDCl_3$) δ 177.1, 66.1, 58.0, 38.4, 31.0, 23.3, 21.0, 18.0. HR-FAB-MS (M + H + gly - $2H_2O$; obtained in a glycerol matrix) calcd for $C_{11}H_{21}BNO_5$ 258.1512; Found: 258.1515.

### 1.4.3.10 Synthesis of 2-(3-Oxocyclopentyl)malonic Acid Diethyl Ester, 20.[155]

A dry 250 mL three-necked round-bottomed flask was charged with diethyl malonate (4.6 mL, 30mmol) in anhydrous ethanol (21 mL) under a nitrogen atmosphere. The solution was cooled to -5 °C and sodium ethoxide in ethanol (0.1 mL, 0.28 mmol) was added. After stirring the reaction mixture for 30 min, 2-cyclopentene-1-one (2.57 mL, 30 mmol) in 20 mL ethanol was added dropwise at -5 °C. After the addition was complete,

the solution was allowed to warm to room temperature and stirred for 15 h. The reaction mixture was treated with acetic acid (2 mL), and then extracted with EtOAc (3x50 mL). The combined extracts were washed with brine (50 mL), dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography(20% ethyl acetate in hexane) to yield 6.15 g (85.2%) of **20** as a colorless liquid. $^1$H NMR (250 MHz, $CDCl_3$) δ 1.27 (t, $J$ = 7.3 Hz), 1.29 (t, $J$ = 7.1 Hz) 1.66 (m, 1H), 2.02 (dd, $J$ = 18.9 Hz, 1H), 2.11–2.38 (m, 3H), 2.51 (dd, $J$ = 7.3 Hz, 1H), 2.84 (m, 1H), 3.35 (d, $J$ = 9.2 Hz, 1H), 4.22 (m, 4H); $^{13}$C NMR (63 MHz, $CDCl_3$) δ 216.9, 168.0, 167.9, 61.4, 56.3, 42.7, 38.0, 36.1, 27.3, 13.9.

### 1.4.3.11 Synthesis of 2-(1,4-Dioxaspiro[4.4]non-7-yl)malonic Acid Diethyl Ester, 21.[166]

A 250 mL round-bottomed flask equipped with a Dean-Stark apparatus and a reflux condenser was charged with **20** (2.33 g, 9.6 mmol), ethylene glycol (1.07 mL, 19.2 mmol), and *p*-toluenesulfonic acid (500 mg) in benzene (150 mL). The mixture was refluxed at 120 °C (oil bath) for 14 h and the progress of the reaction was monitored by TLC. After 14 h the flask was cooled to room temperature and saturated aqueous $NaHCO_3$ (20 mL) was added. The mixture was transferred to a separatory funnel, washed with $H_2O$ (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a colorless oil. The product was purified by column chromatography (EtOAc:hexanes = 1:20) to yield 2.26 g (82.3%) of **21** as a colorless liquid. $^1$H NMR (250 MHz, $CDCl_3$) δ 1.26 (t, $J$ = 7.3 Hz, 6H), 1.44 (m, 1H), 1.59 (dd. $J$ =8.2, 13.5 Hz, 1H), 1.7–2.0 (m, 3H), 2.09 (dd, $J$ = 7.9, 13.5 Hz, 1H), 2.67 (m, 1H), 3.27 (d, $J$ = 9.9 Hz, 1H), 3.85–3.92 (m, 4H), 4.18, 4.19 (each 2H, q, $J$ = 7.3 Hz); $^{13}$C NMR (63 MHz, $CDCl_3$) δ 168.5, 168.4, 116.09, 64.1, 61.1, 57.0, 40.5, 36.6, 35.4, 28.1, 14.0.

### 1.4.3.12 Synthesis of (1,4-Dioxaspiro[4.4]non-7-yl)acetic Acid Ethyl Ester, 22.[166]

To a solution of KOH (1.8g, 27.9 mmol) in 45 mL anhydrous ethanol was added diester **21** (7.9 g , 27.9 mmol ) in 5 mL anhydrous ethanol under nitrogen. After stirring for 6 h at room temperature, the reaction mixture was quenched with HCl (1.5 mL, 3:1 HCl:$H_2O$) and the ethanol removed under reduced pressure. The residue was added to mixture of 8 g of ice and 2 mL of concentrated HCl. The product was extracted into $CH_2Cl_2$, washed with brine (50 mL), dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure to give a dark yellow liquid. The residue was heated at 160 °C to afford a reddish brown liquid which was purified by silica gel column chromatography (10% ethyl acetate in hexane) to yield 4 g (66.9%) of monoester **22**. $^1$H NMR (250MHz, $CDCl_3$) δ 1.25 (t, $J$ = 7.1 Hz, 3H), 1.34 (m, 1H), 1.50 (dd, $J$ = 8.0, 13.3 Hz, 1H), 1.79–1.96 (m, 3H), 2.09 (dd, $J$ = 8.0, 13.3 Hz, 1H), 2.33–2.36 (m, 3H), 3.86–4.10 (m, 4H), 4.10 (q, $J$ = 7.3 Hz, 2H); $^{13}$C NMR (63 MHz, $CDCl_3$) δ 172.68, 117.5, 64.2, 64.1, 60.1, 42.3, 40.2, 35.8, 33.9, 30.0, 14.1.

### 1.4.3.13 Synthesis of 3-(2-Hydroxyethyl)cyclopentanone, 23.

To a suspension of $LiAlH_4$ (0.32 g, 7.9mmol) in THF (20 mL) at -5 °C was added **22** (1.14g, 5.3 mmol) and the mixture stirred for 40 min at -5 °C and then refluxed for 4h. The mixture again was cooled to -5 °C and then hydrolyzed with water. The organic layer was dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure to give a dark yellow liquid which was purified by silica gel column chromatography (40% ethyl acetate in hexane) to yield 0.102 g (57%) of monoester **23**. $^1$H NMR (250MHz, $CDCl_3$) δ 3.68 (t, $J$ = 13.1, 2H), 1.55–1.89 (m, 4H), 2.14–2.44 (m, 5H); $^{13}$C NMR (63 MHz, $CDCl_3$) δ 219.9, 60.4, 44.7, 38.1, 37.9, 33.5, 29.1. Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.06; H, 9.44.

### 1.4.4 Experimental Procedure for Synthesis and Separation of Diastereoisomers of Unnatural Cyclic Amino Acid, C

#### 1.4.4.1 Synthesis of 3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)cyclopentanone, 24.[181]

In a 250 mL three-necked round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed CuCl (0.098mg, 1 mmol) in DMF (30 mL), tributylphosphine (0.55, 2.2 mmol), and the mixture stirred for 1 h. To the solution was added (with a syringe) cyclopentene-2-one (2.0 g, 0.20 mmol) in 30 mL DMF and bis(pinacolato)diboron (6.1 g, 0.24 mmol). After the mixture was stirred for 14 h at room temperature, water (1.0 mL) was added and the resulting mixture was extracted with ethyl acetate. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by column chromatography (30% ethyl acetate in hexane) ($SiO_2$) to give 4.1 g (83%) of **24**. $^1$H NMR (250 MHz) δ 1.25 (s, 12H), 1.67 (m, 1H), 1.85 (m, 1H), 2.02–2.35 (m, 7H); $^{13}$C NMR δ (63 MHz, $CDCl_3$) 24.6, 25.1, 38.7, 40.0, 83.3, 220.7.

#### 1.4.4.2 Synthesis of 7-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-diaza-spiro[4.4]nonane-2,4-dione, 25.

A 50 mL Ace pressure tube was charged with ketone **24** (3.15 g, 15 mmol), aqueous ethanol (50%, 20 mL), potassium cyanide (2.0 g, 30 mmol), and ammonium carbonate (7.2 g, 75 mmol). The reaction vessel was sealed and heated at 60 °C (oil bath) for 8 h. A light yellow precipitate formed. The mixture was cooled to room temperature and the vessel carefully opened in a fume hood. The mixture was concentrated under reduced pressure and the solid obtained was purified by column chromatography (EtOAc:hexanes = 2:1) to afford 3.1 g (85%) of **25** as a distereoisomeric mixture white solid. $^1$H NMR (63 MHz, DMSO-$d_6$) δ 10.53, (10.47) (s, 1H), 8.19, ( 8.02 ) (s, 1H), 1.40–2.10 (m, 7H),

1.16 (s, 12H); $^{13}C$ (63 MHz, $CDCl_3$) $\delta$ 24.5, 27.0, 37.8, 40.0, 69.3, 82.9, 156.3, 178.8. Exact mass calcd for $C_{13}H_2B_2NO_4$ 280.1597; Found: *m/z* 280.1599.

### 1.4.4.3 Separation of Diastereoisomers of 25, Synthesis of 26 and 27.

To a 500 mL round-bottomed flask equipped with magnetic stirrer was added **24** (2.0 g, 7.14 mmol) and chloroform (25 mL). The solution was heated up to the point where **24** completely dissolved in the chloroform. To the solution, hexanes were added until the solution turned cloudy. While heating the solution a drop of chloroform was again added and the flask was kept at room temperature for 24 h. In order to separate the solid formed, the solution was filtered, and the filtrated concentrated under vacuum to afford a white solid **27** 0.89 g (89%). The Solid left in the 500 mL flask was dried under vacuum to afford **26** 0.85 g (85%).

**Compound 26.**

$^1H$ NMR (300 MHz, DMSO–$d_6$) δ 10.47 (s, 1H), 8.02 (s, 1H), 1.40–2.10 (m, 7H), 1.16 (s, 12H); $^{13}C$ (76 MHz, $CDCl_3$) δ 24.5, 27.2, 37.8, 40.0, 69.7, 82.9, 156.7, 180.0.

Exact mass calcd for $C_{13}H_2B_2NO_4$ 280.1597; Found: *m/z* 280.1599.

**Compound 27.**

$^1H$ NMR (300 MHz, DMSO–$d_6$) δ 10.53, (s, 1H), 8.19 (s, 1H), 1.40–2.10 (m, 7H), 1.16 (s, 12H); $^{13}C$ (76 MHz, $CDCl_3$) δ 24.5, 27.0, 37.8, 40.0, 68.6, 82.9, 156.4, 179.7.

Exact mass calcd for $C_{13}H_2B_2NO_4$ 280.1597; Found: *m/z* 280.1599.

### 1.4.4.4 Synthesis of 1-Amino-3-boronocyclopentanecarboxylic Acid, 28.

Boronohydantoin **26** (420 mg, 1.5 mmol) was placed in a 25-mL Ace pressure tube along with aqueous hydrochloric acid (4 mL, 12 *M*). The tube was sealed and heated to 150 °C (oil bath) for 40 h. It was then cooled to room temperature, carefully opened (Hood!), charcoal added, and the resulting mixture filtered through a pad of Celite. The Celite pad was washed with water. Removal of the water under reduced pressure gave 217 mg (81%) of **28** as a white solid. $^{1}$H NMR ($D_2O$) δ 1.15–1.90 (m, 7H); $^{13}$C NMR. (63 MHz, $CDCl_3$) δ 175.9, 66.9, 39.9, 38.5, 29.1, 26.4. HR-FAB-MS (M + H + gly - $2H_2O$; obtained in a glycerol matrix) calcd for $C_9H_{18}BNO_5$: 230.120; Found: 230.137.

### 1.4.4.5 Synthesis of 1-Amino 3-boronocyclopentanecarboxylic Acid, 29.

Boronohydantoin **27** (420 mg, 1.5 mmol) was placed in a 25 mL Ace pressure tube along with hydrochloric acid (4 mL, 12 *M*). The tube was sealed and heated to 150 °C (oil bath) for 40 h. It was then cooled to room temperature and carefully opened (Hood!), charcoal added, and the resulting mixture filtered through a pad of Celite. The Celite pad was washed with water. Removal of the water under reduced pressure gave 210 mg (81%) of **29** as a white solid. $^{1}$H NMR ($D_2O$) δ 0.62–1.45 (m, 7H); $^{13}$C NMR. (63 MHz, $CDCl_3$) δ 176.0, 66.9, 40.7, 38.3, 29.03, 27.6. HR-FAB-MS (M + H + gly - $2H_2O$; obtained in a glycerol matrix) calcd for $C_9H_{18}BNO_5$: 230.120; Found: 230.137.

### 1.4.5 Experimental Procedure for Unnatural Cyclic Amino Acid, D.

### 1.4.5.1 Synthesis of Hydantoin of 3-Allyl-cyclopentanone, 30.[167]

A 50 mL Ace pressure tube was charged with ketone **12** (1.9 g, 15 mmol), aqueous ethanol (50%, 20 mL), potassium cyanide (2.0 g, 30 mmol), and ammonium carbonate (7.2 g, 75 mmol). The reaction vessel was sealed and heated at 60 °C (oil bath) for 8 h. A

light yellow precipitate formed. The mixture was cooled to room temperature and the vessel carefully opened in a fume hood. The mixture was concentrated under reduced pressure and the solid obtained was purified by column chromatography (EtOAc: hexanes = 2:1) to afford 2.15 g (74%) of **30** as a white solid. $^{1}$H NMR (DMSO, $d_6$) δ 9.94 (s, 1H), 8.19 (s, 1H), 5.69–7.71 (m, 1H), 4.93–5.04 (m, 2H), 1.16–2.49 (m, 9H); $^{13}$C NMR. (63 MHz, $CDCl_3$) δ 179.0, 158.2, 137.4, 115.6, 68.2, 43.3, 42.5, 31.1, 30.8.

### 1.4.5.2 Synthesis of Boronohydantoin, 31.

Diisopinocampheylborane, $(Ipc)_2BH$, was prepared according to the literature procedure.[186] A 100 mL round-bottomed flask was fitted with a septum and a magnetic stirring bar and connected to a nitrogen bubbler. The flask was flushed with nitrogen and held at a positive static pressure of nitrogen. Borane-THF (50 mmol, 50 mL, 1.0 *M*) was added to the flask, which was cooled to 0 °C, then (*R*)-pinene (18.4 mL, 115 mmol) was added slowly and the mixture stirred at 0 °C for 1 h. The reaction was maintained at 0 °C for 3 days to give the required crystalline product. Compound **30** (485 mg, 2.5 mmol) was placed in a 150mL round-bottomed flask and dissolved in THF (10 mL) at 0 °C. $(Ipc)_2BH$ (7.5 mmol) in THF (10 mL) was added dropwise via a syringe. The mixture was allowed to warm to room temperature and stirred for 16 h. Freshly distilled acetaldehyde (12 mmol) was added and the mixture stirred for an additional 12 h. Excess acetaldehyde was removed under vacuum and the mixture hydrolyzed with aqueous hydrochloric acid (5 mL, 2.0 *M*). The mixture was extracted with EtOAc (3x30 mL) and the combined organic phase dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (methanol) to afford 372 mg (62%) of **31** as a white solid. $^{1}$H NMR (DMSO, $d_6$) δ 9.94 (s, 1H), 8.18 (s, 1H), 1.12–2.49 (m, 11H), 0.55 (s, 2H); $^{13}$C NMR. (63 MHz, $CDCl_3$) δ 179.7, 156.2, 68.2, 67.7, 43.8, 43.1, 31.2, 23.0. HR-FAB-MS (M + H + gly - $2H_2O$; obtained in a glycerol matrix) calcd for $C_{13}H_{22}BN_2O_5$: 297.1623, Found: 297.1624.

### 1.4.5.3 Synthesis of 1-Amino-3-[(dihydroxyboryl)butyl]cyclopentanecarboxylic Acid, D.

Boronohydantoin **31** (360 mg, 1.5 mmol) was placed in a 25-mL Ace pressure tube along with hydrochloric acid (4 mL, 12 *M*). The tube was sealed and heated to 150 °C (oil bath) for 40 h. It was then cooled to room temperature and carefully opened (Hood!), charcoal added, and the resulting mixture filtered through a pad of Celite. The Celite pad was washed with water. Removal of the water under reduced pressure gave 260 mg (82%) of **31** as a white solid. $^{1}$H NMR ($D_2O$) δ 1.22–2.03 (m, 11H), 0.69 (m, 2H); $^{13}$C NMR. (63 MHz, $CDCl_3$) δ 177.9, 67.2, 45, 42.7, 41, 38.8, 34.2, 24.9, 16.1. HR-FAB-MS (M + H + gly - $2H_2O$; obtained in a glycerol matrix) calcd for $C_{10}H_{26}BN_2O_4$: 272.166, Found: 272.167.

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**PART TWO**

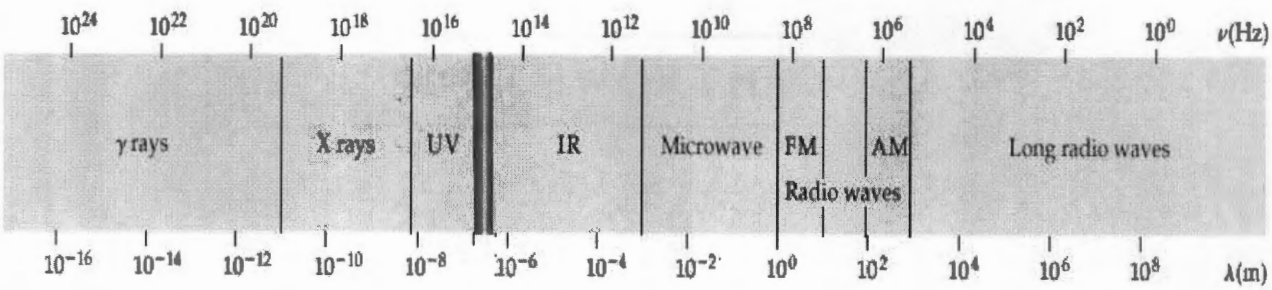
# Microwave-enhanced Reactions Using Organotrifluoroborates

# CHAPTER 1 MICROWAVE THEORY

## 2.1.1 Introduction

In recent years, microwave irradiation has gained importance in organic chemistry and in material processing.[1-6] Microwaves are also used in the area of superconductors and magnetoresistors, the preparation of oxides, nitrides and chalcogenides, production of nanomaterials, and ceramic joining.[7-10] Microwaves have been used in chemistry since the late 1970s, but their use in organic reactions was not seen until the late 1980s. A typical microwave is shown in Figure 2.1.1. Microwave-enhanced reactions are energy efficient, demonstrate enhanced reaction rates, and generally lead to high product yields. Internal settings in microwave dose not allow the temperature to go above the fixed value at which the reaction is carried out even if the time is increased. Microwave irradiation is electromagnetic irradiation in the frequency range of 0.3 to 300 GHz. A typical electromagnetic spectrum is shown in Figure 2.1.2. To avoid interfering with most cellular phone frequencies, all microwave reactors used in chemical synthesis operate at a frequency of 2.45 GHz. It is known that the energy of the microwave photon is in this frequency region is low (0.0016 eV) and not sufficient to cleave chemical bonds and hence it can be said that microwaves cannot induce chemical reactions. Typical microwave reactions are carried out in the or in closed vessels. Microwave-enhanced chemistry is based on the phenomenon called microwave dielectric heating which is dependent on the ability of a material (generally solvent or reagent) to absorb microwave energy and convert it to heat.[11,12] When the sample is irradiated at microwave frequencies, it causes the dipoles or ions to align in the applied electric field. As soon as the applied field starts oscillating, the dipole or ion field also attempts to realign itself with the changing electric field. Energy is lost in the form of heat during this process and the amount of heat produced is directly proportional to the ability of the medium to align itself with the frequency of the applied field. Whenever the dipole does not realign

Figure 2.1.1 Microwave Instrument




2.1.2 Electromagnetic Spectrum

quickly with the applied field, no heating results.[13,14] Generally a reaction medium with the ability to convert electromagnetic energy into heat is required for efficient absorption and for rapid heating. Transfer of energy into the system is slow in case of thermal heating as it depends on the thermal conductivity of the various materials that must be penetrated. This results in the temperature of the reaction vessel being higher than that of the reaction mixture. But, in the case of microwave irradiation, effective internal heating by direct coupling of microwave energy with the molecules of reagents, and solvents is generated which enhances the reaction rates.[15]

### 2.1.2 Microwave Effects

The observed microwave enhancements compared to traditional thermal heating have led to discussions on the existence of non thermal or specific microwave effects.[16,17] In the majority of cases, the observed increase in reaction rate is due to kinetic/thermal effects which result in rapid generation of high reaction temperatures. Non thermal effects results from dipole–dipole interactions between polar molecules and the electromagnetic field. Solvents which can rapidly absorb microwave radiation can be superheated. For example, methanol, which is a high microwave absorbing solvent, can be rapidly heated to temperatures above its boiling point. Ionic liquids have also been used as solvents in microwaves, these liquids can be heated to very high temperatures in few seconds.[16] Such effects are very difficult to produce with thermal heating. Baghurst and Mingos have shown that processes which requires 68 days to reach 90% conversion at 278 $^{0}$C will show the same level of conversion within 1.61 seconds when carried out at 27 $^{0}$C using microwaves.[17] Superheating affects solvents at atmospheric pressure.[18] The formation of "molecular radiators" by direct coupling of microwave energy to specific reagents [19] are examples of specific microwave effects. The rate enhancement by microwaves results from material-wave interactions resulting in thermal effects and specific (non-purely thermal) effects. Many researchers believe that a combination of these two contributions is responsible for the observed effects.

### 2.1.3 Medium Effects

Solvent effects are of prime importance in polar solvents.[20,21] The major interaction occurs between microwaves and polar molecules of the solvent and the energy transfer takes place from the solvent molecules to the reactants. In such cases, specific microwave effects on the reactants are usually masked by solvent absorption.[22] In non-polar solvents such as xylene, and toluene (which are transparent to microwaves) specific absorption by the reactants occurs. In cases where reactants are polar, energy transfer occurs from the reactants to the solvent.[23, 24] Microwave effects are also seen under solvent free conditions, which are safe, cost effective, and environmental friendly.[25]

### 2.1.4 Use of Microwaves in Organic Reactions

#### 2.1.4.1 Heck Reaction

The Heck reaction is a palladium-catalyzed vinylic substitution which is typically carried out between alkenes and an unsaturated halides or triflates. It is a widely used reaction for carbon-carbon bond formation.[26] The first microwave assisted Heck reaction was reported in 1996.[27] A general example of the Heck reaction involving aryl bromides and acrylic acid to get the corresponding cinnamic acids is shown in the Figure 2.1.4.1. Over the years, various groups have studied microwave assisted Heck reactions. Recently microwave assisted Heck reactions in ionic liquid have been reported.[28] Heck reactions under microwave conditions are much faster than under the thermal conditions.

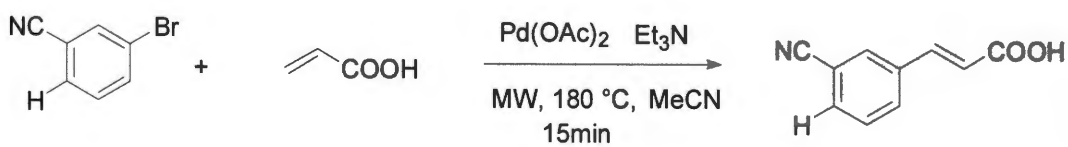



Figure – 2.1.4.1

### 2.1.4.2. Suzuki Reaction

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The Suzuki cross-coupling reaction is one of the most versatile and commonly used methods for the selective construction of carbon-carbon bonds.[29,30] There are numerous reports of Suzuki cross-coupling reactions under microwave conditions.[31-,37] Suzuki reactions can be carried out using water as a solvent under microwave conditions. The advantage of using water is that it is inexpensive; water is also environment friendly. Leadbeater has recently reported rapid, ligand-free palladium-catalyzed aqueous Suzuki couplings with arylboronic acids (Figure 2.1.4.2).[38] He reported that the microwave reactions under microwave condition can be performed on a large scale.[39] There are now a large number of boronic acids available commercially which makes the Suzuki reaction very attractive in organic synthesis.

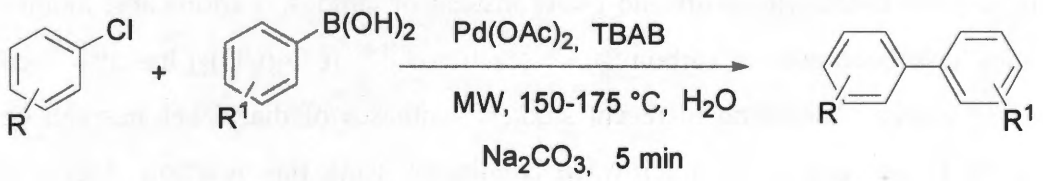



Figure 2.1.4.2

### 2.1.4.3 Sonogashira and Stille Coupling Reactions.

Sonogashira reaction involve palladium/copper catalyzed coupling of terminal acetylenes with aryl or vinyl halides.[40] A microwave assisted Sonogashira coupling reaction was first reported by Erdmlyi and Gogoll.[41] Various examples of Sonogashira couplings in the derivatization of pyrazinones [33] and pyrimidines [42] have been reported under microwave conditions. The Stille coupling reaction is a palladium-catalyzed coupling an organotin compound with organic halide. The first microwave assisted Stille coupling reaction was reported in 2002.[43]

### 2.1.4.4 Carbonylation Reactions

Molybdenum hexacarbonyl is used as a solid precursor of carbon monoxide. Molybdenum hexacarbonyl liberates CO *in situ* when heated at high temperatures. Larhed and co-workers have reported microwave assisted palladium-catalyzed carbonylation reactions.[44,45] These reactions are used in the preparation of amides in good yields. Various simple modifications of the reaction conditions and reagents have been carried out to yield carboxylic acids and esters instead of amides. Various aryl iodides and bromides have been used in carbonylation reactions.[45, 46] $[CO_2(CO)_8]$ has also been used as a CO source. According to recent studies, syntheses of diaryl ketones can be carried out in 10 seconds under microwave conditions using this reaction (Figure – 2.1.4.3.)

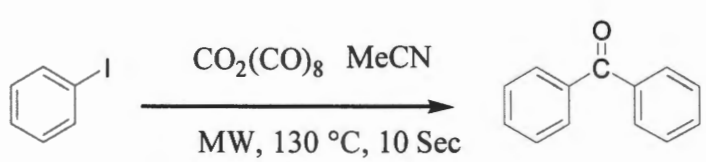



Figure – 2.1.4.3

### 2.1.4.5 Synthesis of Heterocycles

The synthesis of heterocycles can be achieved through cyclocondensation reactions. These reactions, under thermal conditions, require high temperatures and long reaction times.[47] Some of the cyclocondensation reactions require several hours so these reactions are well suited for microwave conditions. Molteni *et al.* have reported three-component, one pot syntheses of fused pyrazoles under microwave conditions using water as a solvent, they occur in one minute (Figure 2.1.4). Over the years various groups have studied microwave assisted synthesis of various heterocycles.[48 -50]

### 2.1.4.6 Mannich Reaction

The Mannich reaction was first reported in the early 1900s. It is an important protocol for the synthesis of β-amino ketones (Fig. 2.1.4.5). Though this reaction is powerful, the reaction suffers from the drastic conditions and long reaction time required. Luthman and coworkers reported microwave assisted Mannich reactions.[51] With their procedure, the desired β-amino ketones can be prepared in 8-10 minutes in good yields. Leadbeater reported a Mannich reaction, which involved condensation of an aldehyde with a secondary amine and a terminal acetylene in the presence of a copper catalyst. Petasis reported a multicomponent reaction which is similarly to Mannich reaction under microwave conditions.[52]

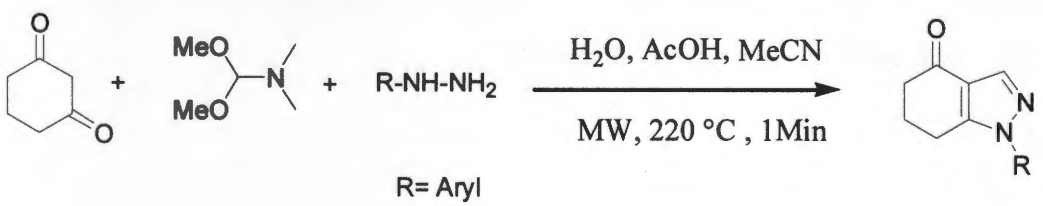



Figure 2.1.4.4

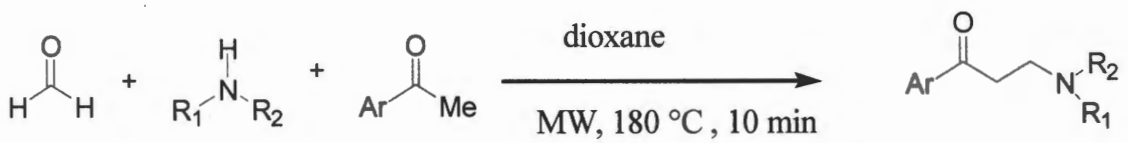



Figure 2.1.4.5.

### 2.1.5 Organotrifluoroborates in Microwave-Enhanced Cross-Coupling Reactions

Organotrifluoroborates have the formula $[R_nBF_{4-n}]^-$ where $n \leq 3$. They had been mere laboratory curiosities since 1940.[52] Thierig, Umland,[53] and Vedejs *et al.*[54] first reported that hydroxyl groups of arylboronic acids could be replaced with fluoride using potassium hydrogen difluoride ($KHF_2$), leading to formation of potassium aryl trifluoroborates (Figure 2.1.5.1); later a slight modification of the original method resulted in organotrifluoroborates being generated in good yields and in pure form (Figure 2.1.5.2).[55] Since that time, there has been a growing interest in the use of organotrifluoroborates in cross-coupling reactions. Cross-coupling reactions are useful for the selective construction of carbon-carbon bonds and provide a convenient pathway to a range of pharmaceuticals, herbicides, natural products, polymers, and liquid crystalline materials.[56-61] The Suzuki-Miyaura cross-coupling reaction is one of the most versatile and commonly used methods for the selective construction of carbon-carbon bonds.[62-66] Suzuki-Miyaura cross-coupling is valued because boron compounds have several advantages over other organometallic compounds, including ease of accessibility, minimal toxicity, and other environmental factors. [67-69]

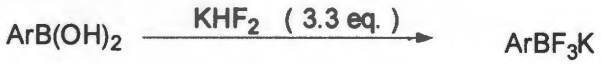



Figure 2.1.5.1

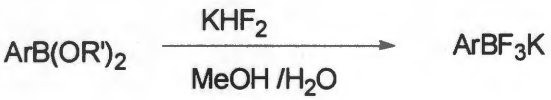



Figure 2.1.5.2 Modified method

Various boron reagents are used in coupling reactions. There are however several problems with boron reagents; for example, vinylboronic acid can be lost via polymerization side reactions. Furthermore, vinylboronic esters are not always selective in cross-coupling reactions, often yielding mixtures of Suzuki–Miyaura and Heck coupled products.[70,71] Recent studies have shown that potassium alkenyltrifluoroborates and alkynyltrifluoroborates offer solutions to a number of problems that sometimes occur with other organoboron reagents in coupling reactions.[72-76] In addition to being crystalline and air stable solids, organotrifluoroborates are easy to isolate and yet remain quite reactive which makes them valuable starting materials for palladium-catalyzed cross-coupling reactions compared to corresponding boronic acid derivatives.[77] Along with the use of alkyl- and aryltrifluoroborates, coupling reactions using heteroaryltrifluoroborates as coupling partners have also been reported. This section of the dissertation deals with the use of aryl, alkenyl- and alkynyltrifluoroborates in microwave-enhanced coupling reactions.

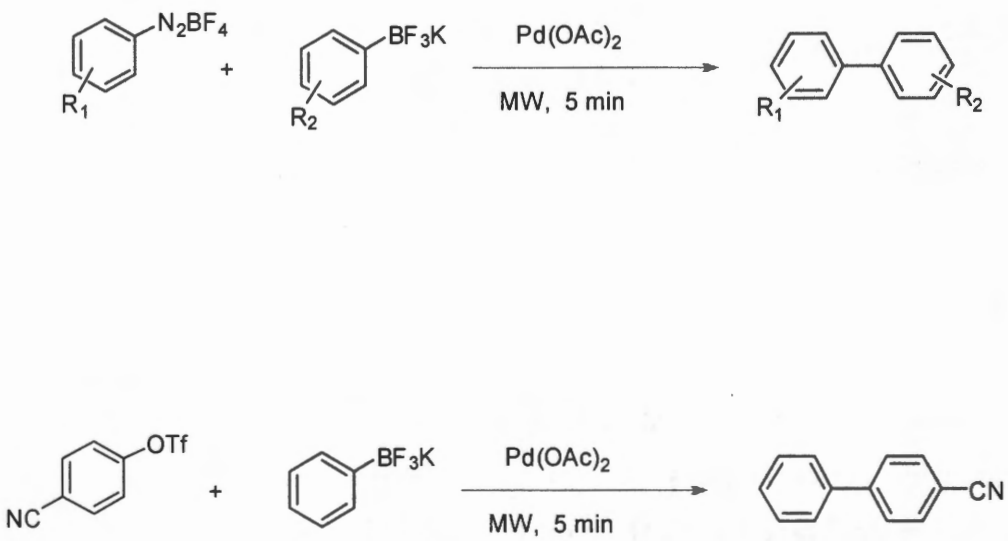



Figure 2.1.5.3 Microwave-enhanced coupling reactions reported by our group

# CHAPTER 2

# MICROWAVE-ENHANCED CROSS-COUPLING REACTIONS INVOLVING ALKENYL- AND ALKYNYLTRIFLUOROBORATES

## 2.2.1 Introduction.

Palladium–catalyzed cross-coupling reactions are commonly used in organic chemistry.[62] Boron reagents such as *B*-alkynyl-9-BBN "ate" complexes have been coupled with a variety of aryl bromides[78] (Figure 2.2.1.1). However these complexes have some disadvantages.[79,80] Cross-coupling reactions of alkynyltrialkoxyborate with aryl bromides have been also reported. Alkenyltrifluoroborates and alkynyltrifluoroborates offer solutions to a number of problems that sometimes occur with other organoboron reagents in coupling reactions.[67-69] Molander reported the use of organotrifluoroborates in coupling reactions in the presence of $Pd(dppf)Cl_2$ as a catalyst.[81] Recently, we reported the first use of microwaves in cross-coupling reactions using potassium aryltrifluroborates.[82] As part of ongoing studies on microwave assisted Suzuki coupling reactions, we initiated a study of the behavior of alkenyl- and alkynyltrifluoroborates under microwave conditions.

## 2.2.2 Results and Discussion

In an effort to optimize reaction conditions, the reaction of potassium (phenylethynyl)trifluroborate and 4-cyanophenyl triflate was examined. Reactions using $Pd_2dba_3.CHCl_3$/dppf, $Pd_2dba_3$/(o-toyl)$_3$, $Pd(OAc)_2$/dppf, and $Pd(OAc)_2$ as catalysts gave moderate yields. Molander successfully coupled potassium alkynyltrifluoroborates with aryl triflates using $PdCl_2(dppf)CH_2Cl_2$ under thermal conditions.[76f] It was found that under microwave conditions $PdCl_2(dppf)CH_2Cl_2$ also gave better yields than other Pd-catalysts. In the absence of a palladium catalyst, no coupling product was observed. (Table 2.2.1, entry 5).

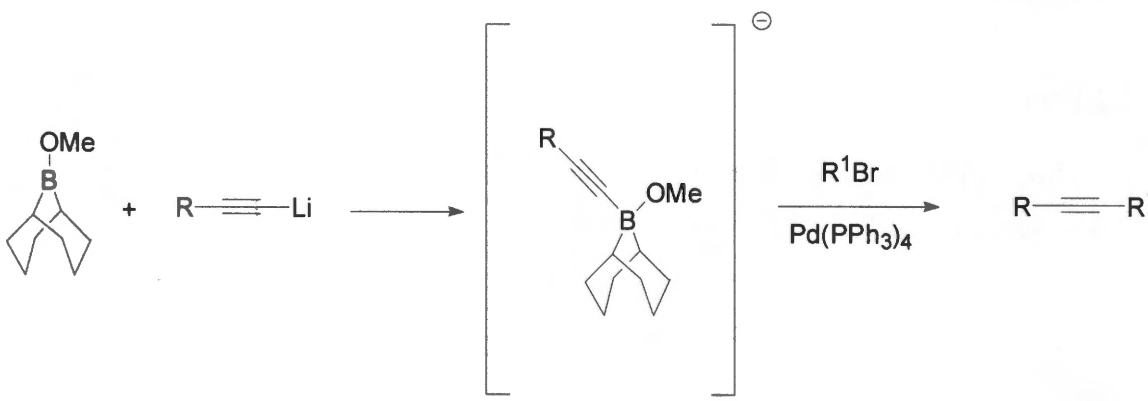
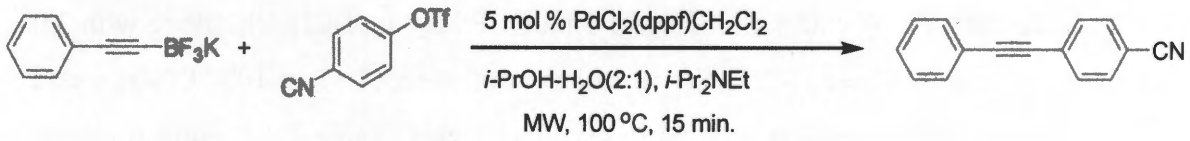



Figure 2.2.1.1 Reaction of B-alkynyl-9-BBN complex and organotrifluoroborate

Table : 2.2.1 Reaction of potassium (phenylethynyl)trifluroborate, and 4-cyanophenyl triflates [a]




| Entry | Base | Conditions | Catalyst | Solvent | Yields( %)[b] |
|---|---|---|---|---|---|
| 1 | $CsCO_3$ | MW-15 min | $Pd(OAc)_2$ | THF- Water | 45 |
| 2 | $CsCO_3$ | MW-15 min | $Pd_2dba_3.CHCl_3$ | *i*-PrOH- water | 50 |
| 3 | Hunig's base | MW-15 min | $PdCl_2(dppf)CH_2Cl_2$ | THF- Water | 67 |
| 4 | Hunig's base | MW-15 min | $PdCl_2(dppf)CH_2Cl_2$ | Water | 0 |
| 5 | Hunig's base | MW-15 min | No catalyst | *i*-PrOH- water | 0 |
| 6 | Hunig's base | MW-15 min | $PdCl_2(dppf)CH_2Cl_2$ | *i*-PrOH- water | 91 |
| 7 | Hunig's base | MW-10 min | $PdCl_2(dppf)CH_2Cl_2$ | *i*-PrOH- water | 80 |
| 8 | $K_2CO_3$ | MW-15 min | $Pd_2dba_3.CHCl_3$ | i-PrOH-water | 60 |

[a] All reactions were carried out at 100 °C

[b] All yields are of pure products isolated by silica gel chromatography

Reactions did not occur in water (Table 2.2.1, entry 4) whereas a mixture of THF-$H_2O$ (2:1) gave moderate yields (67%). Hunig's base (*i*-$Pr_2NEt$), was found to be the most effective for this reaction. Decreasing the reaction time to 10 min gave lower yields (Table 2.2.1, entry 7). A catalyst loading of 5 mol% $PdCl_2(dppf)CH_2Cl_2$, along with 3.0 equivalents of Hunig's base (*i*-Pr2NEt), in isopropanol/water (2:1), at 100 °C was found to provide the coupled products in good to excellent yields (Table 2.2.1, entry 6). After optimization of reaction conditions, we explored the cross-coupling of various alkenyltrifluoroborates (Table 2.2.3), electron-withdrawing groups present in the triflates led to the highest yields (Table 2.2.3, entry 2). Electron-withdrawing groups in the alkenyltrifluoroborates also enhanced the yields (Table 2.2.3, entry 4). We also explored the coupling reaction of various alkynyltrifluoroborates with aryl triflates (Table 2.2.2). Triflates with electron-withdrawing groups successfully coupled with different alkynyltrifluoroborates in good yields (Table 2.2.2, entries 1-4). Triflates containing electron-donating groups gave lower yields than the non-substituted triflates (Table 2.2.2, entries 5 and 6).

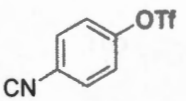
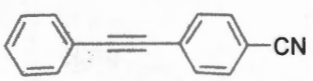
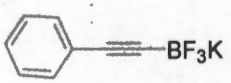
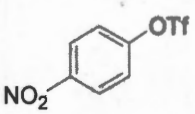
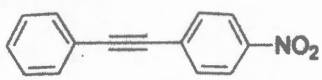
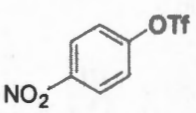
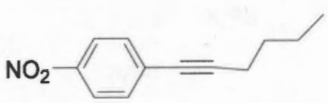
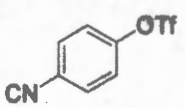
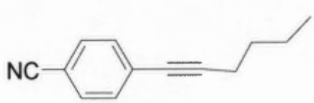
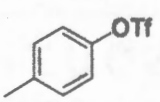
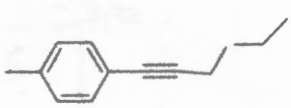
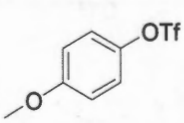
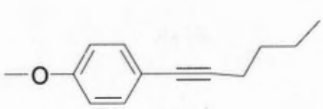
### 2.2.3 Conclusion

In conclusion, an efficient method for coupling of alkenyl-and alkynyltrifluoroborates with various aryl triflates in presence of a palladium catalyst and diisopropyl ethyl amine has been developed using microwave irradiation. The reaction procedure is fast and straightforward and the yields are good.

### 2.2.4 Experimental Section

All glassware was dried in an oven at 120 °C and flushed with dry nitrogen. $^1H$ NMR and $^{13}C$ NMR were recorded in $CDCl_3$ on a Varian 300MHz instrument with chemical shifts

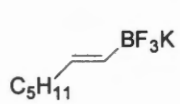
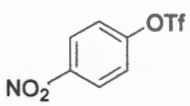
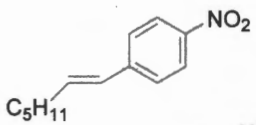
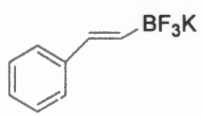
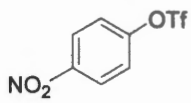
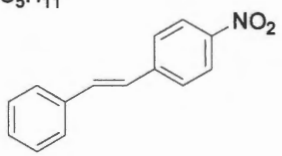
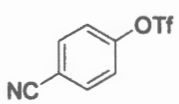
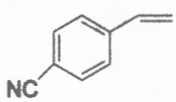
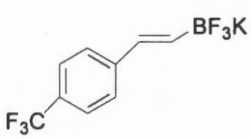
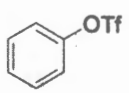
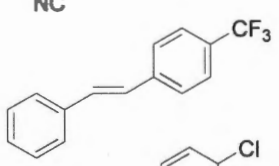
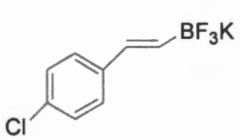
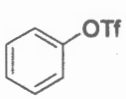
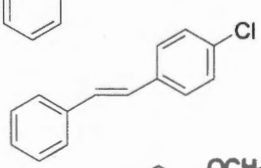
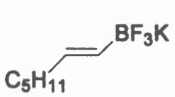
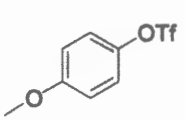
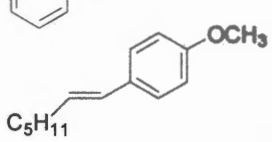
Table 2.2.2 Coupling Reactions of Alkynyltrifluoroborates [a]

| Entry | $R_1BF_3K$ | $R_2$-OTf | $R_1$-$R_2$ | Yields( %)[b] |
|---|---|---|---|---|
| 1 |  |  |  | 91 |
| 2 |  |  |  | 96 |
| 3 |  |  |  | 94 |
| 4 |  |  |  | 90 |
| 5 |  |  |  | 79 |
| 6 |  |  |  | 65 |

[a] All reactions were carried out at 100 °C

[b] All yields are of pure products isolated by silica gel chromatography

Table 2.2.3. Coupling Reactions of alkenyltrifluoroborates

| Entry | $R_1BF_3K$ | $R_2$-OTf | $R_1$-$R_2$ | Yields (%) [b] |
|---|---|---|---|---|
| 1 |  |  |  | 91 |
| 2 |  |  |  | 96 |
| 3 |  |  |  | 94 |
| 4 |  |  |  | 90 |
| 5 |  |  |  | 79 |
| 6 |  |  |  | 65 |

[a] All reactions were carried out at 100 °C

[b] All yields are of pure products isolated by silica gel chromatography

reported relative to TMS. Potassium organotrifluoroborates were prepared utilizing literature methods. In a typical experiment, the organotrifluoroborate (0.55 mmol) and palladium catalyst (5 mole %) were placed in an argon flushed Pyrex tube. The aryl triflate (0.50 mmol) was then added along with diisopropyl ethyl amine (1.5 mmol) and 5 mL of isopropanol/water (2:1). The Pyrex tube was then capped with a rubber septum, placed in a CEM microwave unit, and allowed to react at 100 °C for 15 min. The product was isolated by adding water (15 mL) and ether (15 mL), the ether layer separated, the solvent removed under reduced pressure, and the product isolated by column chromatography.

### 2.2.4.1 General Procedure for the Preparation of Potassium (1-Hexyn-1-yl) trifluoroborate.

A solution of 1-hexyne (0.82 g, 10 mmol, 1 equiv) in 20 mL of dry THF was cooled to -78 °C under argon. *n*-butyllithium (10 mmol, 6.25 mL, 1.6 *M* in hexane, 1 equiv) was added dropwise, and the solution was stirred for 1 h at this temperature. Trimethylborate (15 mmol, 1.56 g, 1.5 equiv) was then added dropwise at -78 °C. The solution was stirred at this temperature for 1 h after which it was allowed to warm to -20 °C for 1 h. A saturated aqueous solution of potassium hydrogen difluoride (60 mmol, 4.7 g, 6.0 equiv) was added to the vigorously stirred solution. The resulting mixture was allowed to stir for 1 h at -20 °C after which it was allowed to warm to room temperature for 1 h. The solvent was removed under reduced pressure, and the resulting white solid was dried under high vacuum for 2 h to remove all water. The solid was then washed sequentially with acetone and with hot acetone. The resulting organic solution was filtered, and the solvent was removed to afford a fluffy white solid. This solid was then dissolved in hot acetone and precipitated with diethyl ether, after which the solution was cooled to -20 °C to complete precipitation of the solid. The product was collected as a white crystalline solid (1.66 g, 78%). The spectrum obtained were in agreement with previously reported data.[81]

### 2.2.4.2 Representative Procedure for the Coupling Reaction of Potassium (1-Hexyn-1-yl)trifluoroborate, and 4-Acetylphenyl Triflates under Microwave Condition

In a typical experiment, the potassium (1-hexyn-1-yl)trifluoroborate (0.55 mmol, 103 mg) and palladium catalyst (5 mole %, 20 mg ) were placed in an argon flushed Pyrex tube. The 4-acetylphenyl trifluoromethanesulfonate (0.50 mmol, 134 mg) was then added along with diisopropyl ethyl amine (1.5 mmol, 0.26 mL) and 5 mL of isopropanol/water (2:1). The Pyrex tube was then capped with a rubber septum, placed in a CEM microwave unit, and allowed to react at 100 °C for 15 min. The product was isolated by adding water (15 mL) and ether (15 mL), the ether layer separated, the solvent removed under reduced pressure, and the product isolated by column chromatography. (69.3 mg, 67%), The spectra obtained are in agreement with previously reported data: $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.88 (dd, $J$ = 6.7, 2.0 Hz, 2H), 7.47 (dd, $J$ = 6.7, 1.9 Hz, 2H), 2.58 (s, 3H), 2.44 (t, $J$ = 7.1 Hz, 2H), 1.62-1.59 (m, 2H), 1.50–1.47 (m, 2H), 0.95 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) $\delta$ 197.4, 135.6, 131.6, 129.2, 128.1, 94.4, 80.1, 30.6, 26.6, 22.0, 19.2, 13.6.

### 2.2.5 Analytical Data

**4-(Phenylethynyl)benzonitrile, 2-1.**[81]

$^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.56 (dm, $J$ = 6.7 Hz, 2H), 7.45 (dm, $J$ = 6.7 Hz, 2H), 2.42 (t, $J$ = 7.1 Hz, 2H), 1.62–1.56 (m, 2H), 1.50–1.42 (m, 2H), 0.94 (t, $J$ = 7.3Hz, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) $\delta$ 132.0, 131.8, 129.1, 118.6, 110.7, 95.6, 79.3, 30.4, 21.9, 19.1, 13.5.

**1-Nitro-4-(phenylethynyl)benzene, 2-2.**[83]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.35–7.44 (m, 3H), 7.52–7.59 (m, 2H), 7.67 (d, $J$ = 8.9 Hz, 2H), 8.23 (d, $J$ = 8.9 Hz, 2H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 87.6, 94.7, 122.1, 123.7, 128.6, 129.3, 130.3, 131.9, 132.3, 147.0.

**1-(Hex-1-ynyl)-4-nitrobenzene, 2-3.**[81]

$^1$H NMR (300 MHz, $CDCl_3$) δ 8.14 (dm, $J$ = 7.5 Hz, 2H), 7.51 (dm, $J$ = 8.5 Hz, 2H), 2.44 (t, $J$ = 7.1 Hz, 2H), 1.63–1.57 (m, 2H), 1.50–1.45 (m, 2H), 0.95 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 146.5, 132.2, 131.2, 123.4, 96.7, 79.2, 30.4, 22.0, 19.2, 13.5.

**1-(Hex-1-ynyl)-4-isocyanobenzene, 2-4.**[81]

$^1$H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H), 1.44–1.51 (m, 2H), 1.55–1.62 (m, 2H), 2.43 (t, 2H), 7.44 (d, $J$ = 8.1 Hz, 2H), 7.56 (d, $J$ = 8.1 Hz, 2H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 13.5, 19.1, 21.9, 30.4, 79.4, 95.5, 110.6, 118.5, 129.0, 131.8, 131.

**1-(Hex-1-ynyl)-4-methylbenzene, 2-5.**[81]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, $J$ = 8.4 Hz, 2H), 7.08 (d, $J$ = 8.4 Hz, 2H), 2.39 (t, $J$ = 7.2 Hz, 2H), 2.33 (s, 3H), 1.58–1.48 (m, 4H), 0.94 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 137.3, 131.3, 128.9, 120.9, 89.5, 80.5, 30.9, 22.0, 21.4, 19.1, 13.7.

**1-(Hex-1-ynyl)-4-methoxybenzene, 2-6.**[81]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, $J$ = 8.7 Hz, 2H), 6.81 (d, $J$ = 8.7 Hz, 2H), 3.78 (s, 3H), 2.39 (t, $J$ = 7.2 Hz, 2H), 1.58–1.48 (m, 4H), 0.94 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 158.9, 132.8, 116.2, 113.7, 88.7, 80.2, 55.2, 30.9, 22.0, 19.1, 13.7.

**(*E*)-1-(Hept-1-enyl)-4-nitrobenzene, 2-7.**[84]

$^1$H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, $J$ = 8.8, 2 H), 7.45 (d, $J$ = 8.6, 2 H), 6.44 (m, 2 H), 2.26 (qd, $J$ = 7.2, 2.8, 2 H), 1.49 (m, $J$ = 7.3, 2H), 1.33 (m, 4 H), 0.91 (t, $J$ = 7.3, 3 H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 146.3, 144.5, 136.7, 128.0, 126.3, 123.9, 33.2, 31.4, 28.6, 22.5, 14.0.

**(*E*)-1-Nitro-4-styrylbenzene, 2-8.**[85]

$^1$H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, $J$ = 8.8 Hz, 2H), 7.64 (d, $J$ = 8.8 Hz, 2H), 7.58 (d, $J$ = 7.4 Hz, 2H), 7.43 (t, $J$ = 7.5 Hz, 2H), 7.37 (t, $J$ = 7.3 Hz, 1H), 7.29 (d, $J$ = 16.3 Hz, 1H), 7.16 (d, $J$ = 16.3 Hz, 1H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 146.9, 143.9, 136.3, 133.4, 128.9, 128.8, 127.0, 126.8, 126.3, 124.0.

**1-Isocyano-4-vinylbenzene, 2-9.**[77b]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.8 (dd, $J$ = 8.8 Hz, 4H), 7.7 (dd, $J$ = 7.2.8 Hz, 1H), 7.2 (d, $J$ = 7.4 Hz, 2H), 5.9 (dd, $J$ = 7.4 Hz, 1H), 5.4 (dd, $J$ = 7.3 Hz, 1H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 142.4, 133.8, 127.0, 119.0, 119.7, 111.1.

**(*E*)-1-Styryl-4-(trifluoromethyl)benzene, 2-10.**[86]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, $J$ = 16.3 Hz, 1H), 7.22 (d, $J$ = 16.3 Hz, 1H), 7.31-7.63 (m, 9H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 124.2, 125.6, 126.5, 126.8, 128.8, 129.9, 127.1, 128.3, 131.2, 136.3, 140.8.

**(*E*)-1-Chloro-4-styrylbenzene, 2-11.**[87]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, $J$ = 16.6 Hz, 1H), 7.06 (d, $J$ =16.6 Hz, 1H), 7.20-7.60 (m, 9H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 126.5, 127.3, 127.6, 127.8, 128.7, 128.8, 129.3, 133.1, 135.8, 137.0.

**(*E*)-1-(Hept-1-enyl)-4-methoxybenzene, 2-12.**[84]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, $J$ = 8.5, 2H), 6.84 (d, $J$ = 8.8, 2H), 6.32 (d, $J$ = 15.9, 1H), 6.09 (dt, $J$ = 15.7, 6.9, 1H), 3.80 (s, 3H), 2.18 (qd, $J$ =6.8, 1.5, 2H), 1.46 (d, $J$ = 7.3, 2H), 1.32 (m, 4H), 0.90 (t, $J$ = 7.1, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 158.5, 130.7, 129.1, 128.9, 126.9, 113.8, 55.2, 33.0, 31.4, 29.2, 22.6, 14.1.

# CHAPTER 3

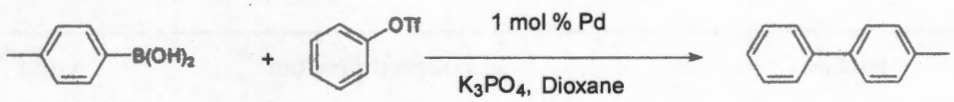
# MICROWAVE-ACCELERATED LIGAND- AND BASE-FREE CROSS-COUPLING REACTION OF POTASSIUM ARYL-TRIFLUORBORTES WITH ARYL-TRIFLATES

## 2.3.1 Introduction

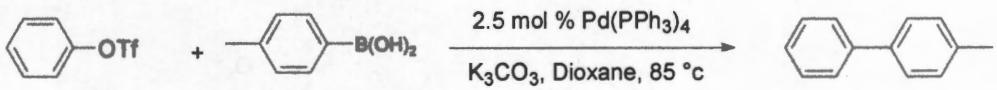
Biaryls are commonly found in biologically important compounds and materials.[62 -66] Over the years various groups have coupled aryltrifluoroborates with various electrophiles like aryl iodides, chlorides, bromides, arenediazonium tetrafluoroborates. The triflates are important partners in the cross-coupling reaction, as they can be easily made from phenols. Although the cross-coupling reactions with organic halides have been studied widely, it is known that trifluoromethanesulfonates (triflates) undergo a clean coupling with organoboron compounds similar to reactions involving organostannanes regents.[88] We have previously studied microwave-enhanced Suzuki coupling reactions of triflates with alkenyl and alkynyltrifluoroborates. As part of ongoing study on microwave assisted Suzuki coupling reactions, we initiated a study of the behavior of aryltrifluoroborates with aryltriflates under microwave conditions. Some of the reported procedures for the synthesis of biaryls are shown in Fig. 2.3.1.

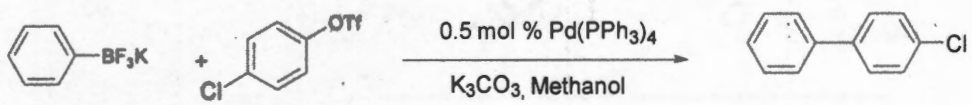
## 2.3.2 Results and Discussion

In an effort to optimize reaction conditions, the reaction of potassium *p*-tolytrifluoroborate and 4-cyanophenyl triflate was first examined. Reactions using $Pd_2dba_3.CHCl_3$/dppf, $Pd_2dba_3$/(o-toyl)$_3$, and $Pd(OAc)_2$/dppf gave moderate yields. $Pd(OAc)_2$ was found to be an effective catalyst. In the absence of a palladium–catalyst, no reaction took place. The scope of the reaction was then studied by coupling potassium *p*-tolytrifluoroborates with various aryl triflates (Table 2.3.1).




Polymer supported Pd-catalyst in synthesis of Biaryls



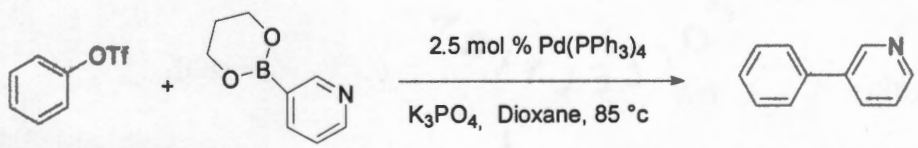
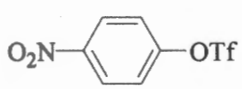
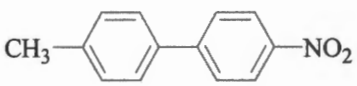
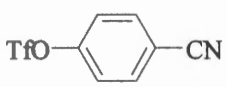
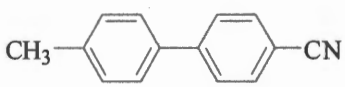
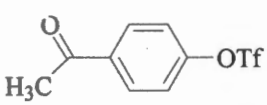
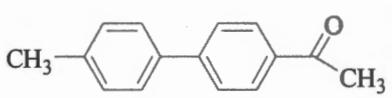
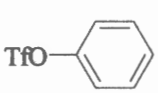
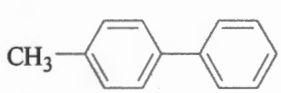
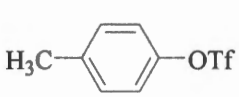
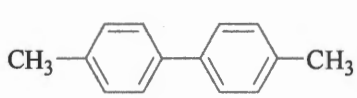
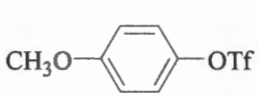
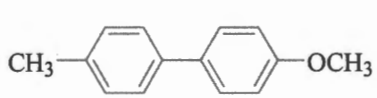




Figure 2.3.1 Some of the reported procedures for the synthesis of biaryls from aryltriflates

Table- 2.3.1 Microwave-enhanced cross-coupling reactions of potassium *p*-tolytrifluorobate with aryl triflate [a]

| Entry | triflate | coupled product | yield [b] |
|---|---|---|---|
| 1 |  |  | 88 |
| 2 |  |  | 85 |
| 3 |  |  | 94 |
| 4 |  |  | 92 |
| 5 |  |  | 63 |
| 6 |  |  | 61 |

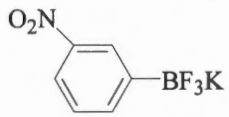
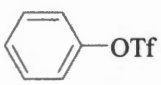
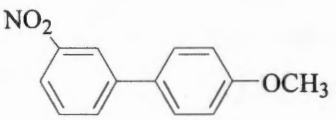
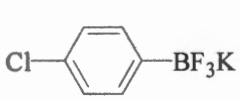
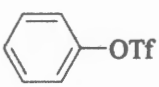
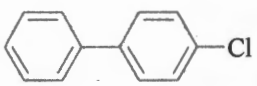
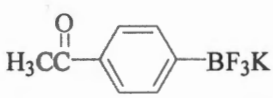
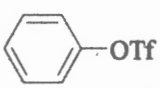
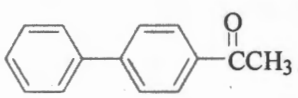
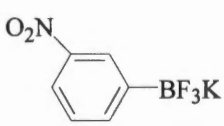
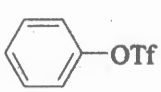
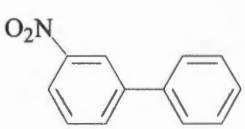
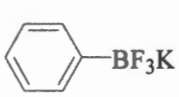
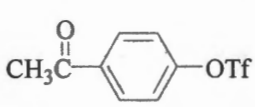
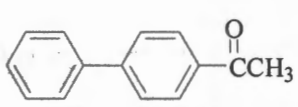
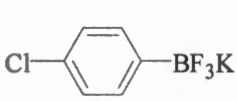
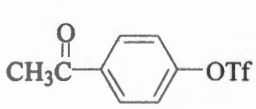
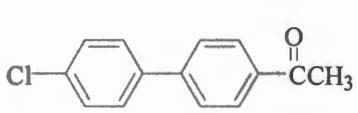
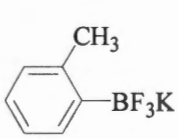
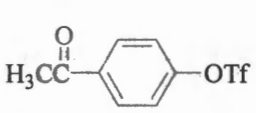
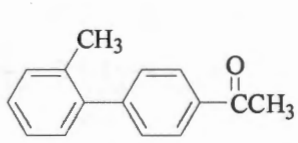
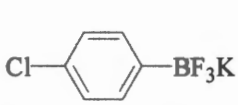
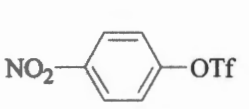
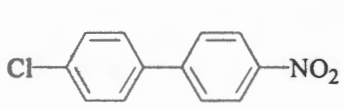
[a]All products were identified by $^{1}H$, $^{13}C$ NMR, and by comparison with authentic samples. [b]Isolated yields.

Aryl triflates containing electron-withdrawing groups (Table 2.3.1, entries 1–3), electron-donating groups (Table 2.3.1, entries 5 and 6), and neutral groups (Table 2.3.1, entry 4) were successfully coupled with potassium *p*-tolytrifluoroborate to give the resultant products in good yields. Recently Molander reported ligand-free Suzuki–Miyaura coupling reaction but this reaction was found to be applicable only to electron-deficient aryl triflates.[89a] Only traces of product were isolated from cross-coupling reactions of electron rich aryl triflates such as *p*-methoxyphenyl triflate. After successfully using *p*-tolytrifluoroborates as coupling partners, other aryltrifluoroborate salts were also investigated. (Table2.3.2). Excellent yields were achieved in most cases. Potassium aryltrifluoroborates having electron-withdrawing (Table 2.3.2, entries 2,3), electron neutral (Table 2.3.2, entry 5), and electron-donating (Table 2.3.2, entries 1,10) groups all reacted with the aryl triflates to produce the expected products in good yields. Coupling products were obtained from *ortho*-substituted substrates in moderate yields. Steric hindrance appears to have little impact on the cross-coupling reaction. Even in the case of highly hindered 2,6-dimethylphenyltrifluoroborate, the desired product was obtained in a 56% yield. Notably, the reaction conditions are mild and the reactants tolerate a variety of functionality such as carbonyl, nitriles, halide, and nitro groups.

### 2.3.3 Conclusion

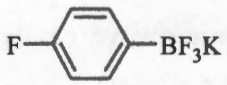
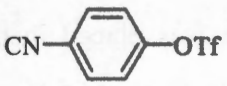
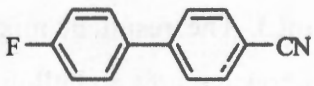
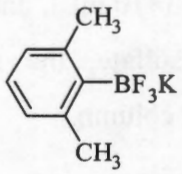
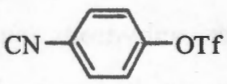
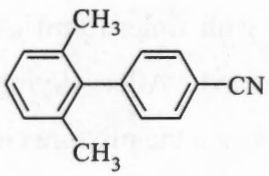
In conclusion, we have developed a protocol for the synthesis of biaryl products utilizing the palladium-catalyzed cross-coupling of potassium organotrifluoroborates with aryl triflates in aqueous ethanol in the absence of a base or ligand under microwave irradiation. The desired products were obtained in good to excellent yields within 15 minutes, whereas the same reactions required several hours under thermal conditions. The advantages of the microwaves include short reaction times, fewer side reactions, and higher product yields, when compared to conventional Suzuki–Miyaura cross-coupling reactions of boronic acids.

Table 2.3.2. Microwave-enhanced cross-coupling reactions.

| Entry | aryl trifluroborate | triflate | coupled product | yield [b] |
|---|---|---|---|---|
| 1 |  |  |  | 95 |
| 2 |  |  |  | 98 |
| 3 |  |  |  | 60 |
| 4 |  |  |  | 50 |
| 5 |  |  |  | 90 |
| 6 |  |  |  | 89 |
| 7 |  |  |  | 85 |
| 8 |  |  |  | 86 |

[a]All products were identified by $^{1}H$ NMR, $^{13}C$, NMR, and by comparison with authentic samples. [b]Isolated yields.

Table2.3.2. Microwave-enhanced cross-coupling reactions (contd.)

| Entry | aryl trifluroborate | triflate | coupled product | yield [b] |
|---|---|---|---|---|
| 9 |  |  |  | 95 |
| 10 |  |  |  | 56 |

[a]All products were identified by $^{1}H$ NMR, $^{13}C$, NMR, and by comparison with authentic samples. [b]Isolated yields.

### 2.3.4 Experimental Section

All glassware was dried in an oven at 120 °C and flushed with dry nitrogen. $^{1}H$ NMR and $^{13}C$ NMR were recorded in $CDCl_3$ on a Varian 300 MHz instrument with chemical shifts reported relative to TMS. Potassium organotrifluoroborate (0.55 mmol), aryltriflate (0.50 mmol), and $Pd(OAc)_2$ (1.2 mol %) were dissolved in aqueous ethanol (1:1 by volume; 5 mL). The resultant mixture was placed in the microwave cavity of a CEM discover microwave unit and allowed to react at 95 °C for 15 min. The reaction mixture was diluted with water (5 mL), extracted with ethyl acetate (3×10 mL), and the organic phase separated. After drying over anhydrous sodium sulfate, the solution was concentrated, and the mixture chromatographed over silica gel column.

#### 2.3.4.1 Representative Procedure for the Synthesis of Potassium *p*-Tolytrifluoroborate.

*p*-Tolylboronic acid (3.78 mmol, 5.13 g) and potassium hydrogen fluoride (10.3 mmol, 8.03 g) were placed in a 100 mL round-bottomed flasked along with water (50 mL) and methanol (25 mL) and the mixture stirred for 3 hr. The resulting slurry was taken up in acetone and evaporated under reduced pressure on a rotary evaporator. The resulting solid was dissolved in acetone, filtered, and the solution dried over sodium sulfate. The solvent was then evaporated under reduced pressure on a rotary evaporator, redissolved in a minimum amount of hot acetone, and allowed to cool. Ethyl ether was added until no cloudiness was observed in the supernatant. The solid was filtered and washed with ethyl ether. Partial evaporation of the mother liquor and addition of ethyl ether led to the second crop of the product. The obtained solid was dried on high vacuum line to give (4.56 g, 61%) of product.

### 2.3.4.2 Representative Procedure for the Synthesis of 4-Methylbiphenyl

Potassium *p*-tolytrifluoroborate (108 mg, 0.55 mmol), phenyl triflate (113 mg, 0.50 mmol), and $Pd(OAc)_2$ (1.40 mg, 0.60 mol %) were dissolved in aqueous ethanol (1:1 by volume, 5 mL). The resultant mixture was placed in the microwave cavity of a CEM discover microwave unit and allowed to react at 95 °C for 15 min. The reaction mixture was diluted with water (5 mL) extracted with ethyl acetate (3x10 mL), and the organic phase separated. After drying over anhydrous sodium sulfate, the solution was concentrated, and the mixture chromatographed over silica gel column using hexane-ethyl acetate (50:1) as eluent to yield a white solid (77 mg, 92%).

### 2.3.5 Analytical Data

**4-Methyl-4'-nitrobiphenyl, 3-1.**[9]

$^1$H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 7.35 (d, $J$ = 8.0 Hz, 2H), 7.69 (d, $J$ = 8.0 Hz, 2H), 7.94 (d, $J$ = 8.9 Hz, 2H), 8.28 (d, $J$ = 8.9 Hz, 2H); $^{13}$C NMR (76 MHz, CDCl3) $\delta$ 20.7, 124.0, 127.0, 127.4, 129.8, 134.8, 138.7, 146.4, 146.5.

**4'-Methylbiphenyl-4-carbonitrile, 3-2.**[90]

$^1$H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H), 7.32 (d, $J$ = 7.9 Hz, 2H), 7.64 (d, $J$ = 7.9 Hz, 2H), 7.85 (d, $J$ = 8.7 Hz, 2H), 7.89 (d, $J$ = 8.7Hz, 2H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 20.7, 109.6, 118.8, 126.8, 127.2, 129.7, 132.7, 135.3, 138.3.

**1-(4'-Methylbiphenyl-4-yl)ethanone, 3-3.**[91]

$^1$H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, $J$ = 8.0 Hz, 2H), 7.67 (d, $J$ = 8.0 Hz, 2H), 7.63-7.61 (m, 2H), 7.48–7.44 (m, 2H), 7.41–7.37 (m, 1H), 2.62 (s, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 197.7, 145.7, 139.8, 135.8, 128.93, 128.89, 128.2, 127.3, 127.2, 26.6.

**4-Methylbiphenyl, 3-4.**[92]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.63–7.62 (m, 2H), 7.55–7.53 (m, 2H), 7.49-7.45 (m, 2H), 7.38–7.35 (m, 1H), 7.30–7.28 (m, 2H), 2.44 (s, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 141.1, 138.3, 136.9, 129.4, 128.6, 126.89, 126.88, 21.2.

**4,4'-Dimethylbiphenyl, 3-5.**[92]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.47(d, $J$ = 7.6 Hz, 4H), 7.22(d, $J$ = 7.6 Hz, 4H), 2.37 (s, 6H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 138.6, 136.9, 129.7, 127.1, 21.3.

**4-Methoxy-4'-methylbiphenyl, 3-6.**[93]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, $J$ = 8.8 Hz, 2H), 7.44 (d, $J$ = 8.2 Hz, 2H), 7.21 (d, $J$ = 8.2 Hz, 2H), 6.95 (d, $J$ = 8.8 Hz, 2H), 3.81 (s, 3H), 2.37 (s, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 159.2, 138.2, 136.6, 134.0, 129.7, 128.2, 126.8, 114.4, 55.6, 21.3.

**4'-Methoxy-3-nitrobiphenyl, 3-7.**[94]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, $J$ = 7.8 Hz, 2H), 7.52 (d, $J$ =7.8 Hz, 2H), 7.40 (dd, $J$ = 7.8, 8.0 Hz, 2H), 7.29 (t, $J$ = 7.8 Hz, 1H), 6.97 (d, $J$ = 8.0 Hz, 2H), 3.83 (s, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 159.1, 140.8, 133.8, 128.7, 128.2, 126.7, 126.7, 114.2, 55.3.

**4-Chlorobiphenyl, 3-8.**[95a]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.33–7.56 (m, 9H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 126.9, 127.5, 128.3, 128.9, 129.0, 133.3, 139.6, 140.0.

**1-(Biphenyl-4-yl)ethanone, 3-9.**[92]

$^1$H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, $J$ = 8.4 Hz, 2H), 7.68 (d, $J$ = 7.8Hz, 2H), 7.62 (d, $J$ = 7.8 Hz, 2H), 7.46 (dd, $J$ = 7.8, 8.4 Hz, 2H), 7.39 (t, $J$ = 7.2 Hz, 1H), 2.63 (s, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 197.8, 145.8, 139.8, 135.8, 129.0, 128.9, 128.2, 127.3, 127.2, 26.7.

**3-Nitrobiphenyl, 3-10.**[94a]

$^1$H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.21 (d, $J$ = 8 Hz, 1H), 7.91 (d, $J$ = 8 Hz, 1H), 7.65–7.60 (m, 3H), 7.51 (t, $J$ = 8 Hz, 2H), 7.44 (t, $J$ = 7.8 Hz, 1H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 137.5, 129.0, 128.9, 127.9, 126.8.

**1-(Biphenyl-4-yl)ethanone, 3-11.**[92]

$^1$H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, $J$ = 8.4 Hz, 2H), 7.69 (d, $J$ = 8.4 Hz, 2H), 7.64 (d, $J$ = 7.6 Hz, 2H), 7.48 (t, $J$ = 7.6 Hz, 2H), 7.41 (t, $J$ = 7.2 Hz, 1H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 197.8, 145.8, 139.9, 135.8, 128.9, 128.9, 128.2, 127.3, 127.2, 26.7.

**1-(4'-Chlorobiphenyl-4-yl)ethanone, 3-12.**[91]

$^1$H NMR (300 MHz, $CDCl_3$) δ 8.05–7.96 (m, 2H), 7.69–7.53 (m, 4H), 7.05–6.95 (m, 2H), 3.86 (s, 3H), 2.62 (s, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 26.8, 127.3, 127.4, 128.4, 129.0, 129.1, 136.0, 140.0, 145.9, 197.9.

**1-(2'-Methylbiphenyl-4-yl)ethanone, 3-13.**[95a]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.21–7.27 (m, 6H), 6.95 (d, $J$ = 8.4 Hz, 2H), 3.85(s, 3H), 2.28 (s, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 158.8, 141.9, 135.7, 134.7, 130.6, 130.5, 130.2, 127.2, 126.0, 113.8, 55.5, 20.8.

**4-Chloro-4'-nitrobiphenyl, 3-14.**[84]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, $J$ = 8.4 Hz, 2H), 7.56 (d, $J$ = 8.7 Hz, 2H), 7.70 (d, $J$ = 8.7 Hz, 2H), 8.28 (d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 124.09, 127.55, 128.5, 129.3, 135.1, 137.0, 146.1, 147.1.

**4'-Fluorobiphenyl-4-carbonitrile, 3-15.**[90]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.33 (t, $J$ = 8.7 Hz, 2H), 7.80 (dd, $J$ = 5.3 Hz, 8.7 Hz, 2H), 7.86 (d, 2H, $J$ = 8.4 Hz), 7.90 (d, 2H, $J$ = 8.4 Hz); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 110.0, 115.9, 118.7, 127.5, 129.2, 132.8, 134.7, 143.5, 163.8.

**2',6'-dimethylbiphenyl-4-carbonitrile, 3-16.**[94c]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.19–7.28 (m, 3H), 7.7 (dd, 4H, $J$ = 7.8 Hz), 1.96 (s, 6H); 13C NMR (76 MHz, $CDCl_3$) δ 110.7, 118.8, 127.5, 127.8, 129.9, 132.8, 132.2, 135.2, 139.8, 146.2.

# CHAPTER 4

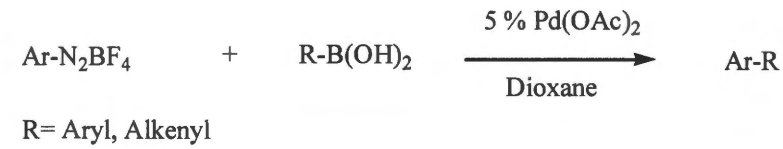
# MICROWAVE-ENHANCED LIGAND- AND BASE-FREE CROSS-COUPLING REACTIONS OF ARENEDIAZONIUM TETRA-FLUOROBORATES

## 2.4.1 Introduction.

Over the years various boron reagents have been used in cross-coupling reactions with arenediazonium tetrafluoroborates. It has been shown that stable arenediazonium tetrafluoroborates, derived from inexpensive and easily accessible aromatic amines, are effective partners in cross-coupling partners with organoboron reagents. [95] According to previously reported work by Darses and Genet, cross-coupling reactions using arenediazonium tetrafluoroborates were found to be limited to sterically unhindered organoboronic acids, and boronic esters did not undergo the cross-coupling reaction.[96] They found that reactions with organotrifluoroborates are more effective than the corresponding boronic acids and esters. We recently reported the base and ligand free microwave-enhanced cross-coupling reaction with aryl triflates.[97] In continuation of this work we explored coupling reactions with aryl trifluoroborates under microwave conditions. Cross-coupling reactions of arenediazonium tetrafluoroborates are shown in Figure 2.4.1.1.

## 2.4.2 Results and Discussion

This study was initiated by reacting 4-methoxybenzenediazonium tetrafluoroborate with potassium phenyltrifluoroborate in the presence of a palladium catalyst. In absence of a palladium catalyst no carbon-carbon bond formation occurred. Various solvents were evaluated for the reaction. Methanol, methanol-water (2:1), dioxane, dioxane-water (2:1), THF, THF-water (2:1), 2-propanol, 2-propanol-water (2:1) were examined. $Pd_2dba_3.CHCl_3$/dppf, $Pd_2dba_3$/(o-toyl)$_3$, $Pd(OAc)_2$/dppf, and $Pd(OAc)_2$ were evaluated as catalysts.





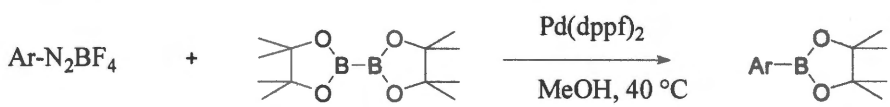



Figure 2.4.1.1 Different Cross-coupling Reactions of Arenediazonium Tetrafluoroborates

The best results were obtained using 2.0 mol% $Pd(OAc)_2$ in 2-propanol at 40 $^0$C under microwave irradiation for 5 minutes. A variety of arenediazonium tetrafluoroborates were then allowed to react with various substituted potassium aryltrifluoroborates to produce the desired products in good to excellent yields. We also carried out the reaction under thermal conditions to determine the effect of microwaves (Table 2.4.2). We found that reactions often require hours to complete under thermal conditions (40 °C). Reaction yields are also higher using microwave irradiation in comparison to those obtained in thermal reactions.[97] The nature of the substituents on the aryltrifluoroborates did not have a major influence on the reaction yields. Substrates bearing electron-donating groups (Table 2.4.1, entries 1 and 6), electron-withdrawing groups (Table 2.4.1, entries 3) and an electronically neutral group (Table 2.4.1, entry 2) were effectively coupled to produce the corresponding products in good yields. Potassium trifluoroborates bearing an *ortho*-substituent or electron-withdrawing groups gave good results but higher temperatures and longer reaction times (10 min) were required (Table 2.4.1, entries 9, 10, and 12). Even in the case of the highly hindered compound like 2,6-dimethylphenyltrifluoroborate, the desired product was obtained in a 52%.

### 2.4.3 Conclusion

In conclusion, the palladium-catalyzed cross-coupling reaction of arenediazonium tetrafluoroborates with potassium aryltrifluoroborate provides a convenient route to biaryl moieties. Reactions are accelerated by use of microwave irradiation. The advantages of the microwave protocol include shorter reaction times, fewer side reactions, and in most of the cases higher product yields, when compared to conventional thermal Suzuki-Miyaura cross-coupling reactions.

Table 2.4.1 . Microwave-enhanced cross-coupling reactions

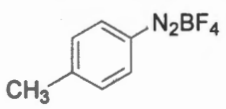
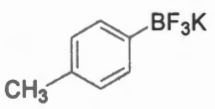
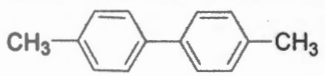
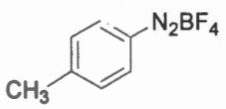
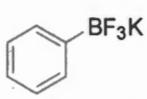
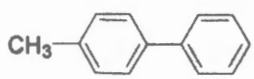
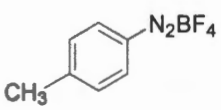
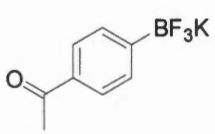
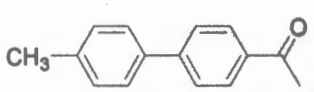
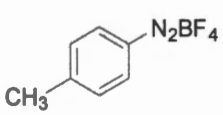
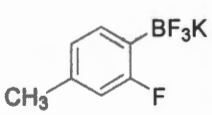
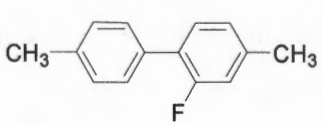
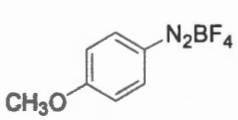
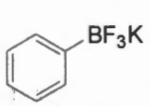
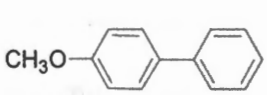
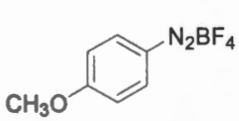
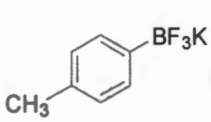
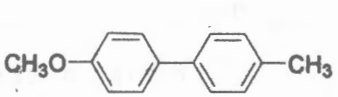
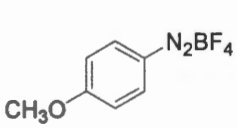
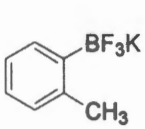
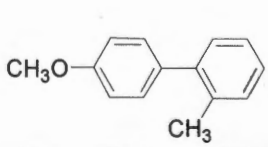
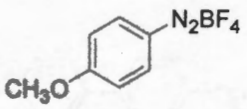
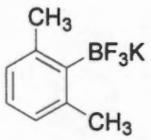
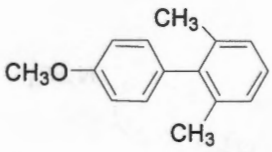
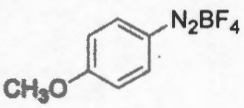
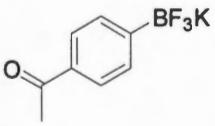
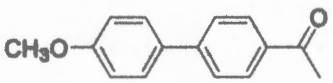
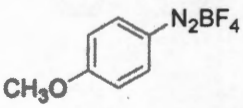
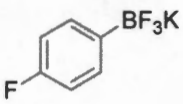
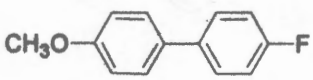
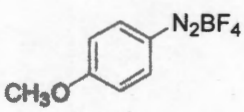
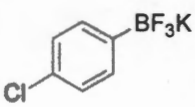
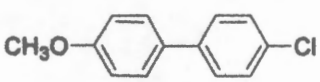
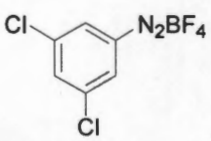
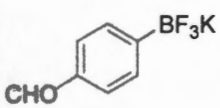
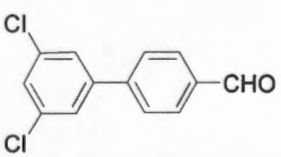
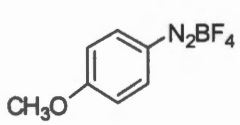
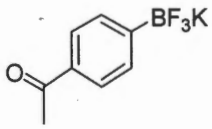
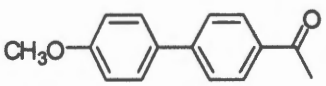
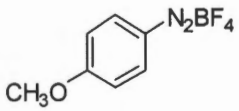
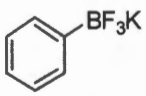
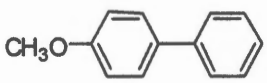
| Entry | Arenediazonium Tetrafluoroboranes | Aryltrifluoroborates | Product[b] | Yield %[c] |
|---|---|---|---|---|
| 1a |  |  |  | 93 |
| 2a |  |  |  | 90 |
| 3d |  |  |  | 57 |
| 4a |  |  |  | 82 |
| 5a |  |  |  | 92 |
| 6a |  |  |  | 86 |
| 7a |  |  |  | 79 |

Table 2.4.1 (contd.)

| Entry | Arenediazonium Tetrafluoroboranes | Aryltrifluoroborates | Product[b] | Yield %[c] |
|---|---|---|---|---|
| 9d |  |  |  | 52 |
| 10d |  |  |  | 51 |
| 11a |  |  |  | 97 |
| 12a |  |  |  | 86 |
| 13a |  |  |  | 93 |

[a] Reactions were run in 2-propanol at 40 °C for 5 min.
[b] All products were identified by $^{1}H$ NMR, $^{13}C$ NMR, and by comparison with authentic samples. [c] Isolated yields. [d] Reactions were run in 2-propanol at 75 °C for 10 min.

Table 2.4.2 Thermal reactions of Tetrafluoroboranes with Aryltrifluroborates

| Entry | Arenediazonium Tetrafluoroboranes | Aryltrifluoroborates | Product[b] | Yield |
|---|---|---|---|---|
| 1a |  |  |  | 25 |
| 2a |  |  |  | 59 |

[a] Reactions were run in 2-propanol at 40 °C for 30 min. under thermal conditions

### 2.4.4 Experimental Section

All glassware was dried in an oven at 120 °C and flushed with dry nitrogen. $^{1}H$ NMR and $^{13}C$ NMR were recorded in $CDCl_3$ on a Varian 300 MHz instrument with chemical shifts reported relative to TMS. Potassium organotrifluoroborate (0.55 mmol), aryltriflate (0.50 mmol), and $Pd(OAc)_2$ (1.2 mol %) were dissolved in aqueous ethanol (1:1 by volume; 5 mL). The resultant mixture was placed in the microwave cavity of a CEM discover microwave unit and allowed to react at 95 °C for 15 min. The reaction mixture was diluted with water (5 mL), extracted with ethyl acetate (3×10 mL), and the organic phase separated. After drying over anhydrous sodium sulfate, the solution was concentrated, and the mixture chromatographed over silica gel column.

#### 2.4.4.1 Represtative Procedure for the Synthesis of Potassium *p*-Tolytrifluoroborate.

*p*-Tolylboronic acid (3.78 mmol, 5.13 g) and potassium hydrogen fluoride (10.28 mmol, 8.03 g) were placed in a 100 mL round-bottomed flask along with water (50 mL) and methanol (25 mL) and the mixture stirred for 3 h. The resulting slurry was taken up in acetone and evaporated under reduced pressure on a rotary evaporator. The solid was dissolved in acetone, filtered, and the organic solution dried over anhydrous sodium sulfate. The solution was then evaporated under reduced pressure on a rotary evaporator, redissolved in minimum amount of hot acetone, and allowed to cool. Ethyl ether was added until no cloudiness was observed in the supernatant. The solid was filtered and washed with ethyl ether. Partial evaporation of mother liquor and addition of ethyl ether led to the second crop of the product. The solid obtained was dried on a high vacuum line to give (4.56 g, 61%) of product.

### 2.4.4.2 Representative Procedure for the Synthesis of 4-Methoxybiphenyl

A dry Pyrex tube fitted with an air-tight rubber cap was charged with 4-methoxybenzenediazonium tetrafluoroborate (133 mg, 0.60 mmol), potassium phenyl-trifluoroborate (92 mg, 0.50 mmol) and $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) while maintaining a nitrogen atmosphere. Nitrogen-purged 1-propanol (3.0 mL) was then added. The resulting mixture was placed in a CEM microwave unit and allowed to react at 40 °C for 5 min. The solution was concentrated under reduced pressure and then purified by column chromatography using hexane-ethyl acetate (100:1) as eluent to yield a white solid (92% yield). All products reported in the Table are known compounds whose physical and spectroscopic data are in accord with values reported in the literature.

### 2.4.5 Analytical Data

**4,4'-Dimethylbiphenyl, 4-1.**[92]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, $J$ = 7.6 Hz, 4H), 7.22 (d, $J$ =7.6 Hz, 4H), 2.37 (s, 6H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 138.6, 136.9, 129.7, 127.1, 21.3.

**4-Methylbiphenyl, 4-2.**[90]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.63–7.62 (m, 2H), 7.55–7.53 (m, 2H), 7.49–7.45 (m, 2H), 7.38–7.35 (m, 1H), 7.30–7.28 (m, 2H), 2.44 (s, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 141.1, 138.3, 136.9, 129.4, 128.6, 126.9, 126.9, 21.2.

**1(4'-Methoxybiphenyl-4-yl)ethanone, 4-3.**[91]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.20–7.03 (m, 5H), 6.96 (dd, $J$ = 2.47, 6.48 Hz, 2H), 3.82 (s, 3H), 2.04 (s, 6H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 158.3, 141.5, 136.5, 133.3, 130.0, 127.2, 126.7, 113.8, 55.2, 20.9.

**2-Fluoro-4'-methylbiphenyl, 4-4.**[99]

$^1$H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3H), 7.11–7.25 (m, 5H), 7.40–7.45 (m, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 21.2, 116.0, 124.3, 128.6, 128.7, 128.8, 129.1, 130.6.

**4-Methoxybiphenyl, 4-5.**[99]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, $J$ = 7.8 Hz, 2H), 7.52 (d, $J$ = 7.8 Hz, 2H), 7.40 (dd, $J$ =7.8, 8.0 Hz, 2H), 7.29 (t, $J$ =7.8 Hz, 1H), 6.97 (d, $J$ = 8.0 Hz, 2H), 3.83 (s, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 159.1, 140.8, 133.8, 128.7, 128.2, 126.7, 126.7, 114.2, 55.3

**4-Methoxy-4'-methylbiphenyl, 4-6.**[96]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, $J$ = 8.8 Hz, 2H), 7.44 (d, $J$ = 8.2 Hz, 2H), 7.21 (d, $J$ = 8.2 Hz, 2H), 6.95 (d, $J$ = 8.8 Hz, 2H), 3.81 (s, 3H), 2.37 (s, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 159.2, 138.2, 136.6, 134.0, 129.7, 128.2, 126.8, 114.4, 55.6, 21.3.

**4'-Methoxy-2-methylbiphenyl, 4-7.**[100]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.25–7.21 (m, 6H), 6.95 (dd, $J$ = 8.8 Hz, 2H), 3.85 (s, 3H), 2.27 (s, 3H), 3.85 (s, 3H), 2.04 (s, 2H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 158.5, 141.5, 135.5, 134.4, 130.3, 130.2, 129.9, 126.9, 125.7, 113.5, 55.3, 20.5

**4'-Methoxy-2,6-dimethylbiphenyl, 4-8.**[111]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.20–7.03 (m, 5H), 6.96 (dd, $J$ = 2.47, 6.48 Hz, 2H), 3.82 (s, 3H), 2.04 (s, 6H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 158.3, 141.5, 136.5, 133.3, 130.0, 127.2, 126.7, 113.8, 55.2, 20.9.

**4- Acetyl-4-methoxybiphenyl, 4-9.**[112]

$^1$H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, $J$ = 8.2 Hz, 2H), 7.65 (d, $J$ = 8.2 Hz, 2H), 7.58 (d, $J$ = 8.6 Hz, 2H), 7.00 (d, $J$ = 8.6 Hz, 2H), 3.87 (s, 3H), 2.63 (s, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 197.7, 159.9, 145.4, 135.3, 132.3, 129.0, 128.4, 126.6, 114.4, 55.4, 26.6.

**4-Fluoro-4'-methoxybiphenyl, 4-10.**[100]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.53–7.46 (m, 4H), 7.10 (dd, $J$ = 8.6, 8.7 Hz, 2H), 6.97 (dd, $J$ = 8.8, 8.7 Hz, 2H), 3.85 (s, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 161.9, 158.9, 136.7, 132.5, 128.0, 127.8, 115.3, 114.1, 55.2.

**4-Chloro-4'-methoxybiphenyl, 4-11.**[100]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.52–7.50 (m, 4H), 7.41–7.36 (m, 2H), 6.93 (d, $J$ = 8.8 Hz, 2H), 3.86 (s, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 159.4, 139.3, 132.7, 132.5, 128.8, 128.0, 127.9, 114.3, 55.3.

**3',5'Dichlorobiphenyl-4-Carbaldehyde, 4-12.**[101]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.99 (dd, $J$ = 7.1 Hz, 2H), 7.70 (dd, $J$ = 7.2 Hz, 2H), 7.47 (t, $J$ = 1.9 Hz, 1H), 7.39 (d, $J$ = 1.9 Hz, 2H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 191.8, 144.4, 142.9, 136.2, 135.8, 130.6, 128.5, 127.9, 126.1

# CHAPTER 5

# MICROWAVE-ENHANCED CROSS-COUPLING REACTIONS INVOLVING ALKYNYLTRIFLUOROBORATES WITH ARYL BROMIDES

## 2.5.1 Introduction.

Palladium-catalyzed alkynylation has emerged as one of the reliable methods for synthesis of alkynes.[102] The most commonly used alkynylation reactions are the copper-promoted Castro- Stephens reaction [103] and the Sonogoshira reaction.[40] Among these the Sonogoshira reaction is generally considered one of the most powerful methods for the preparation of alkynes. This reaction is used widely in natural product synthesis and material science.[104] Over the years, various developments have taken place in order to improve the Sonogoshira reaction. Negishi and coworkers reported the palladium-catalyzed alkynylation reactions of alkynylzincs[105] with of 1-halo-1-alkynes.[106] Palladium-catalyzed alkynylation using alkynylsodiums have also been investigated. But, even with recent developments, there are instances in which Sonogoshira coupling fails to give acceptable yields. Organoboron compounds present several advantages over other organometallic reagents. Organoboron compounds are less toxic when compared to organostannane reagents and they possess remarkable stability compared to alkynylzincs and magnesium reagents.[67-69,107] Previously, Soderquist coupled boron reagents like *B*-alkynyl-9-BBN "ate" complexes with variety of aryl bromides but there are some disadvantages with the use of 9- BBN reagents.[78-80] Suzuki reported cross-coupling of (9-R-9-BBN) reagents with aryl triflates. Cross-coupling reactions of potassium alkenyl-alkynyltrifluoroborates with electrophiles were not satisfactory until Molander reported the use of organotrifluoroborates in the presence of $Pd(dppf)Cl_2$ as a catalyst.[81] Reactions of alkynyltrifluoroborates reported by our group are shown in Fig. 2.5.1.1.

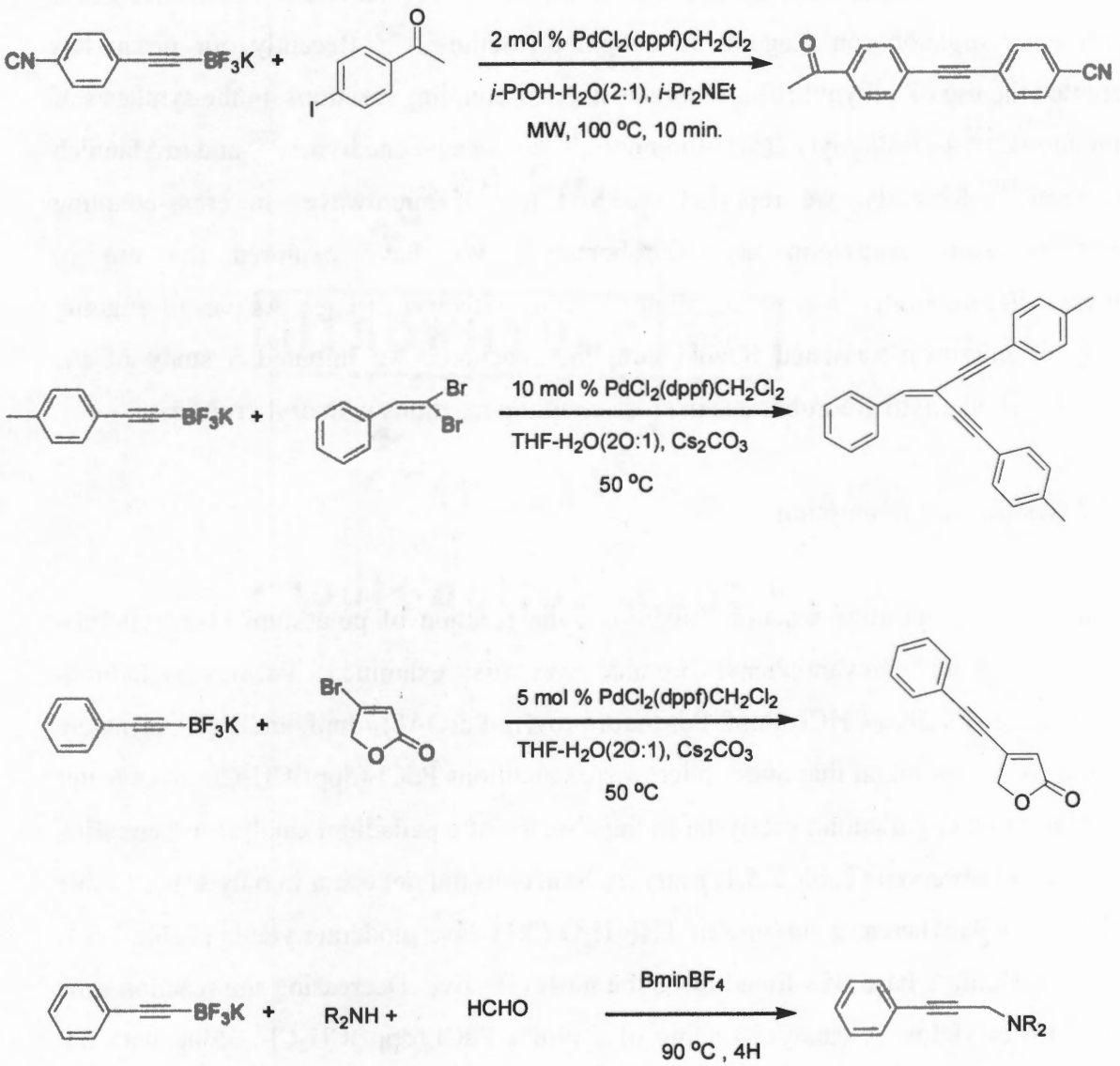


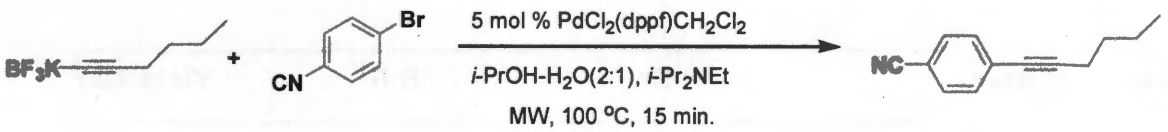

Figure 2.5.1.1 Use of alkynyltrifluoroborates in various reactions reported by our group

Alkynyltrifluoroborates offer solutions to a number of problems that sometimes occur with other organoboron reagents in coupling reactions.[67-69] Recently our group has reported the use of alkynyltrifluoroborates in cross-coupling reactions in the synthesis of coumarins, [108] 4-(1-alkynyl)-2(5H)-furanones,[108] conjugated enediynes,[109] and in Mannich reactions.[110] Recently, we reported the first use of microwaves in cross-coupling reactions using potassium aryltrifluroborates.[82] We have explored the use of alkynyltrifluoroborates in cross-coupling reactions with aryl triflates. As part of ongoing study of microwave-assisted Suzuki coupling reactions, we initiated a study of the behavior of alkynyltrifluoroborates in cross-coupling reactions with aryl bromides.

### 2.5.2 Results and Discussion

In an effort to optimize reaction conditions, the reaction of potassium (1-hexyn-1yl)-trifluroborate and 4-cyanophenyl bromide was first examined. Various palladium-catalysts like $Pd_2dba_3.CHCl_3$/dppf, $Pd_2dba_3$/(o-toyl)$_3$, $Pd(OAc)_2$/dppf, and $Pd(OAc)_2$ were examined. It was found that under microwave conditions $PdCl_2(dppf)CH_2Cl_2$ gives better yields than other palladium catalysts. In the absence of a palladium catalyst, no coupling product was observed (Table 2.5.1, Entry 5). Reactions did not occur in only water (Table 2.5.1, Entry 4) whereas a mixture of THF-$H_2O$ (2:1) gave moderate yields (Table 2.5.1, Entry 3). Hunig's base was found to be the most effective. Decreasing the reaction time led to lower yields. A catalyst loading of 5 mol% $PdCl_2(dppf)CH_2Cl_2$, along with 3.0 equivalents of Hunig's base (*i*-Pr2NEt), in isopropanol/water (2:1), at 100 °C was found to provide the coupled products in good yields (Table 2.5.1, Entry 6). After optimization of reaction conditions, we explored the cross-coupling reaction of potassium (1-hexyn-1yl)trifluroborate with various aryl bromides. (Table 2.5.2).

Table 2.5.1 Reaction of Potassium (1-hexyn-1yl)trifluroborate, and 4-cyanophenyl bromide [a]

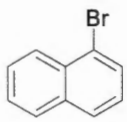
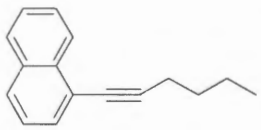
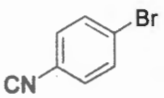
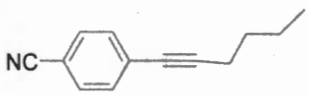
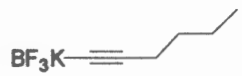
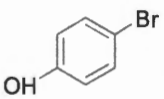
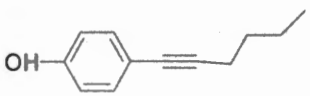
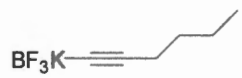
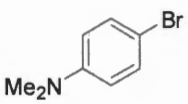
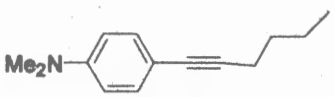
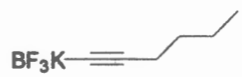
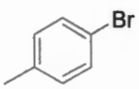
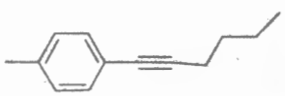



| Entry | Base | Conditions | Catalyst | Solvent | Yields( %)[b] |
|---|---|---|---|---|---|
| 1 | $CsCO_3$ | MW-15 min | $Pd(OAc)_2$ | THF- Water | 44 |
| 2 | $CsCO_3$ | MW-15 min | $Pd_2dba_3.CHCl_3$ | *i*-PrOH- water | 40 |
| 3 | Hunig's base | MW-15 min | $PdCl_2(dppf)CH_2Cl_2$ | THF- Water | 61 |
| 4 | Hunig's base | MW-15 min | $PdCl_2(dppf)CH_2Cl_2$ | Water | 0 |
| 5 | Hunig's base | MW-15 min | No catalyst | *i*-PrOH- water | 0 |
| 6 | Hunig's base | MW-15 min | $PdCl_2(dppf)CH_2Cl_2$ | *i*-PrOH- water | 98 |
| 7 | Hunig's base | MW-10 min | $PdCl_2(dppf)CH_2Cl_2$ | *i*-PrOH- water | 89 |
| 8 | $K_2CO_3$ | MW-15 min | $Pd_2dba_3.CHCl_3$ | i-PrOH-water | 49 |

[a] All reactions were carried out at 100 °C

[b] All yields are of pure products isolated by silica gel chromatography

Table 2.5.2. Cross-coupling reactions involving potassium (1-hexyn-1yl)-trifluroborate with various aryl bromides [a]

| Entry | $R^1BF_3K$ | R-Br | $R-R^1$ | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  |  | 87 |
| 2 |  |  |  | 98 |
| 3 |  |  |  | 74 |
| 4 |  |  |  | 64 |
| 5 |  |  |  | 30 |

[a] All reactions were carried out at 100 °C

[b] All yields are of pure products isolated by silica gel chromatography

Electron-withdrawing groups present in the bromides led to the highest yields (Table 2.5.2, entry 2). Yields with electron-donating group on the bromide gave low yields (Table 2.5.2, entry 5). Better yields were obtained with hydroxyl and, dimethylamine present in the bromides (Table 2.5.2, entry 3,4). We also explored the coupling reaction of various alkynyltrifluoroborates with 4-cyanophenyl bromide (Table 2.5.3). All alkynyltrifluoroborates coupled usefully with 4-cyanophenyl bromide; 2-methylpent-1-en-3-ynyltrifluoroborates gave the highest yield (Table 2.5.3, Entry 3).

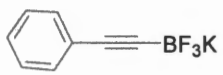
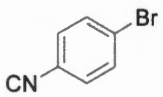
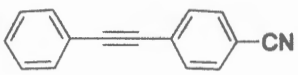
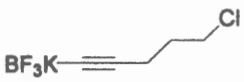
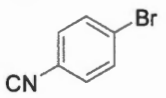
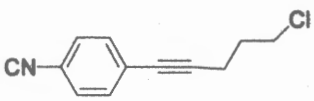
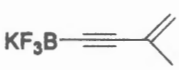
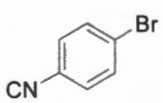
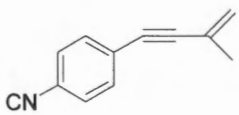
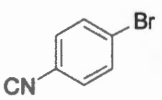
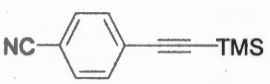
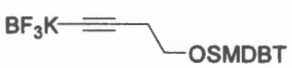
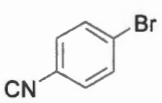
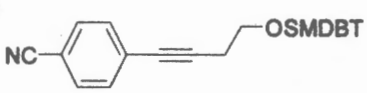
### 2.5.3 Conclusion

In conclusion, an efficient method for coupling alkynyltrifluoroborates with various aryl bromides in the presence of a palladium catalyst and diisopropyl ethyl amine as a base has been developed under microwave irradiation. The reaction procedure is fast and straightforward and the yields are good.

### 2.5.4 Experimental Section

All glassware was dried in an oven at 120 °C and flushed with dry nitrogen. $^{1}H$ NMR and $^{13}C$ NMR were recorded in $CDCl_3$ on a Varian 300 MHz instrument with chemical shifts reported relative to TMS. Potassium organotrifluoroborates were prepared untilizing literature methods. In a typical experiment, the organotrifluoroborate (0.55 mmol) and palladium catalyst (5 mole %) were placed in an argon flushed Pyrex tube. The aryl bromide (0.50 mmol) was then added along with diisopropyl ethyl amine (1.5 mmol) and 5 mL of isopropanol/water (2:1). The Pyrex tube was then capped with a rubber septum, placed in a CEM microwave unit, and allowed to react at 100 °C for 15 minutes. The product was isolated by adding water (15 mL) and ether (15 mL), the ether layer separated, the solvent removed under reduced pressure, and the product isolated by column chromatography.

Table 2.5.3 . Cross-coupling reactions involving various potassium Alkynyltrifluroborate with various 4-cyanophenyl bromide [a]

| Entry | $R^1BF_3K$ | R-Br | $R-R^1$ | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  |  | 70 |
| 2 |  |  |  | 84 |
| 3 |  |  |  | 87 |
| 4 |  |  |  | 61 |
| 5 |  |  |  | 87 |

[a] All reactions were carried out at 100 °C

[b] All yields are of pure products isolated by silica gel chromatography

### 2.5.4.1 Representative Procedure for the Coupling of Potassium (1-Hexyn-1-yl)-trifluoroborate with 4-Cyanophenyl bromide under Microwave Condition.

In a typical experiment, potassium (1-hexyn-1-yl)trifluoroborate (0.55 mmol, 103.4 mg) and the palladium catalyst (5 mole % , 20 mg) were placed in an argon flushed Pyrex tube. The 4-cyanophenyl bromide (0.50 mmol, 95mg) was then added along with di-isopropyl ethyl amine (1.5 mmol, 0.26 mL) and 5 mL of isopropanol/water (2:1). The Pyrex tube was then capped with a rubber septum, placed in a CEM microwave unit, and allowed to react at 100 °C for 15 min. The product was isolated by adding water (15 mL) and ether (15 mL), the ether layer separated, the solvent removed under reduced pressure, and the product isolated by column chromatography (81.7 mg, 98%). The spectra obtained are in agreement with previously reported data: $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.56 (dm, $J$ = 6.7 Hz, 2H), 7.45 (dm, $J$ = 6.7Hz, 2H), 2.42 (t, $J$ = 7.1 Hz, 2H), 1.62–1.56 (m, 2H), 1.50–1.42 (m, 2H), 0.94 (t, $J$ = 7.3Hz, 3H); $^{13}$CNMR (76 MHz, CDCl3) 132.0, 131.8, 129.1, 118.6, 110.7, 95.6, 79.3, 30.4, 21.9, 19.1, 13.5.

### 2.5.5 Analytical Data

**1-(Hex-1-ynyl)naphthalene, 5-1.**[81]

$^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.37 (dd, $J$ = 8.3 Hz, 1H), 7.85 (d, $J$ = 8.1 Hz, 1H), 7.79 (d, $J$ = 8.2 Hz, 1H), 7.64 (d, $J$ = 7.1 Hz, 1H), 7.57 (t, $J$ = 7.0 Hz, 1H), 7.51 (t, $J$ = 7.4 Hz, 1H), 7.41 (t, $J$ = 7.7 Hz, 1H), 2.59 (t, $J$ = 7.1 Hz, 2H), 1.75–1.69 (m, 2H), 1.62–1.55 (m, 2H), 1.01 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 133.5, 133.2, 130.0, 128.2, 127.8, 126.4, 126.3, 126.2, 125.2, 121.8, 95.5, 78.5, 31.0, 22.1, 19.4, 13.7.

**1-(Hex-1-ynyl)-4-isocyanobenzene, 5-2.**[81]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.56 (dm, $J$ = 6.7 Hz, 2H), 7.45 (dm, $J$ = 6.7 Hz, 2H), 2.42 (t, $J$ = 7.1 Hz, 2H), 1.62–1.56 (m, 2H), 1.50–1.42 (m, 2H), 0.94 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 132.0, 131.8, 129.1, 118.6, 110.7, 95.6, 79.3, 30.4, 21.9, 19.1, 13.5.

**4-(Hex-1-ynyl)phenol, 5-3.**[81]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.29 (dd, $J$ = 6.6, 2.1 Hz, 2H), 6.75 (dd, $J$ = 6.6, 2.1 Hz, 2H), 4.78 (s, 1H), 2.39 (t, $J$ = 7.1 Hz, 2H), 1.59–1.56 (m, 2H), 1.49–1.45 (m, 2H), 0.94 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 154.9, 133.1, 116.5, 115.3, 88.8, 80.1, 30.9, 22.0, 19.0, 13.6.

**4-(Hex-1-ynyl)-N,N-dimethylaniline, 5-4.**[81]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, $J$ = 9.0 Hz, 2H), 6.62 (d, $J$ = 8.9 Hz, 2H), 2.95 (s, 6H), 2.39 (t, $J$ = 7.1 Hz, 2H), 1.59–1.54 (m, 2H), 1.49–1.45 (m, 2H), 0.94 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 132.5, 111.9, 87.7, 81.0, 40.3, 31.1, 22.0, 19.2, 13.7

**1-(Hex-1-ynyl)-4-methylbenzene, 5-5.**[81]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, $J$ = 8.1 Hz, 2H), 7.09 (d, $J$ = 7.9 Hz, 2H), 2.40 (t, $J$ = 7.1 Hz, 2H), 2.33 (s, 3H), 1.62–1.56 (m, 2H), 1.54–1.44 (m, 2H), 0.95 (t, $J$ = 7.3 Hz,

3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 137.4, 131.4, 128.9, 121.0, 89.6, 80.5, 30.9, 22.0, 21.4, 19.1, 13.6.

**4-(Phenylethynyl)benzonitrile, 5-6.**[81]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.62 (m, 4H), 7.54 (m, 2H), 7.38 (m, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$)δ 132.1, 132.0, 131.8, 129.1, 128.5, 128.2, 122.2, 118.5, 111.5, 93.8, 87.7.

**1-(5-Chloropent-1-ynyl)-4-isocyanobenzene, 5-7.**[81]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, $J$ = 8.1 Hz, 2H), 7.43 (d, $J$ = 8.2 Hz, 2H), 3.67 (t, $J$ = 6.3 Hz, 2H), 2.61 (t, $J$ = 6.9 Hz, 2H), 2.06–2.01 (m, 2H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 132.0, 131.8, 128.5, 118.4, 111.0, 93.1, 80.1, 43.5, 31.0, 16.8.

**1-Isocyano-4-(3-methylbut-3-en-1-ynyl)benzene,5-8.**[81]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, $J$ = 6.7, 1.8 Hz, 2H), 7.51 (dd, $J$ = 6.6, 1.9 Hz, 2H), 5.46 (q, $J$ = 0.8 Hz, 1H), 5.39–5.37 (m, 1H), 1.99 (t, $J$ = 1.2 Hz, 3H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 132.0, 131.9, 128.2, 126.2, 123.7, 118.5, 111.4, 94.9, 86.6, 23.1;

**4-(Trimethylsilyl)ethynyl)benzonitrile,5-9.**[81]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, $J$ = 8.6 Hz, 2H), 7.54 (d, $J$ = 8.6 Hz, 2H), 0.26 (s, 9H); $^{13}$CNMR (76 MHz, $CDCl_3$) δ 132.4, 131.9, 128.0, 118.4, 111.8, 103.0, 99.6, -0.3.

**4-(Trimethylsilylethynyl)benzonitrile, 5-10.**[81]

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, $J$ = 8.2 Hz, 2H), 7.45 (d, $J$ = 8.3 Hz, 2H), 3.81 (t, $J$ = 6.8 Hz, 2H), 2.64 (t, $J$ = 6.8Hz, 2H), 0.90 (s, 9H), 0.09 (s, 6H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 132.0, 131.9, 128.7, 118.5, 110.9, 92.5, 80.2, 61.5, 25.8, 23.9, 18.3, -5.3.

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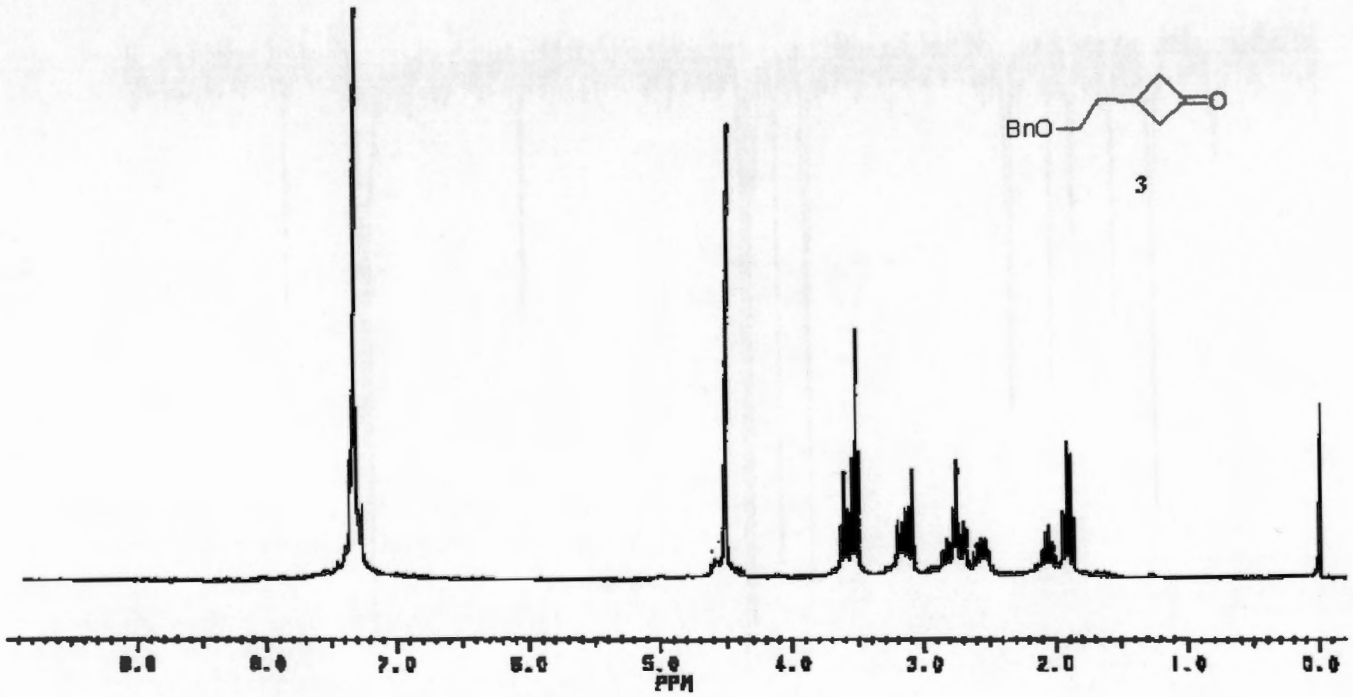
# APPENDIX I

NMR Spectra of Representative, Intermediate and Target Compounds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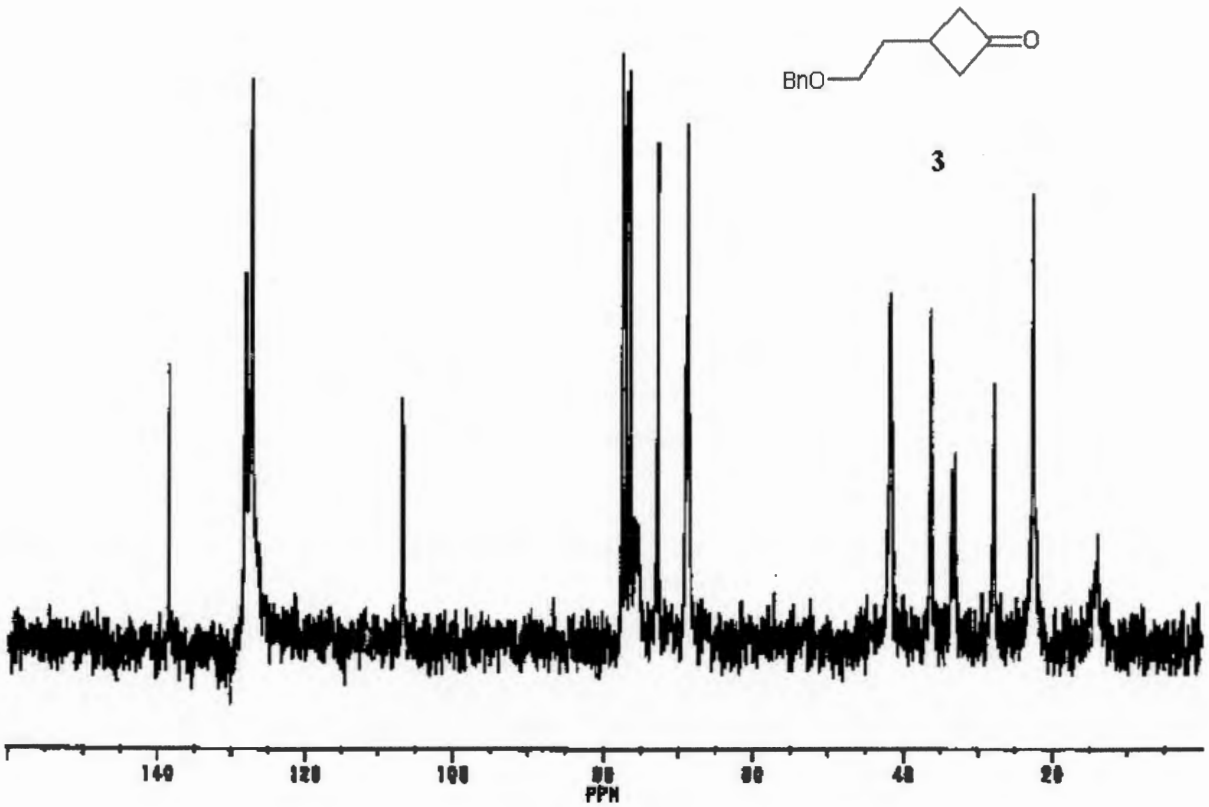
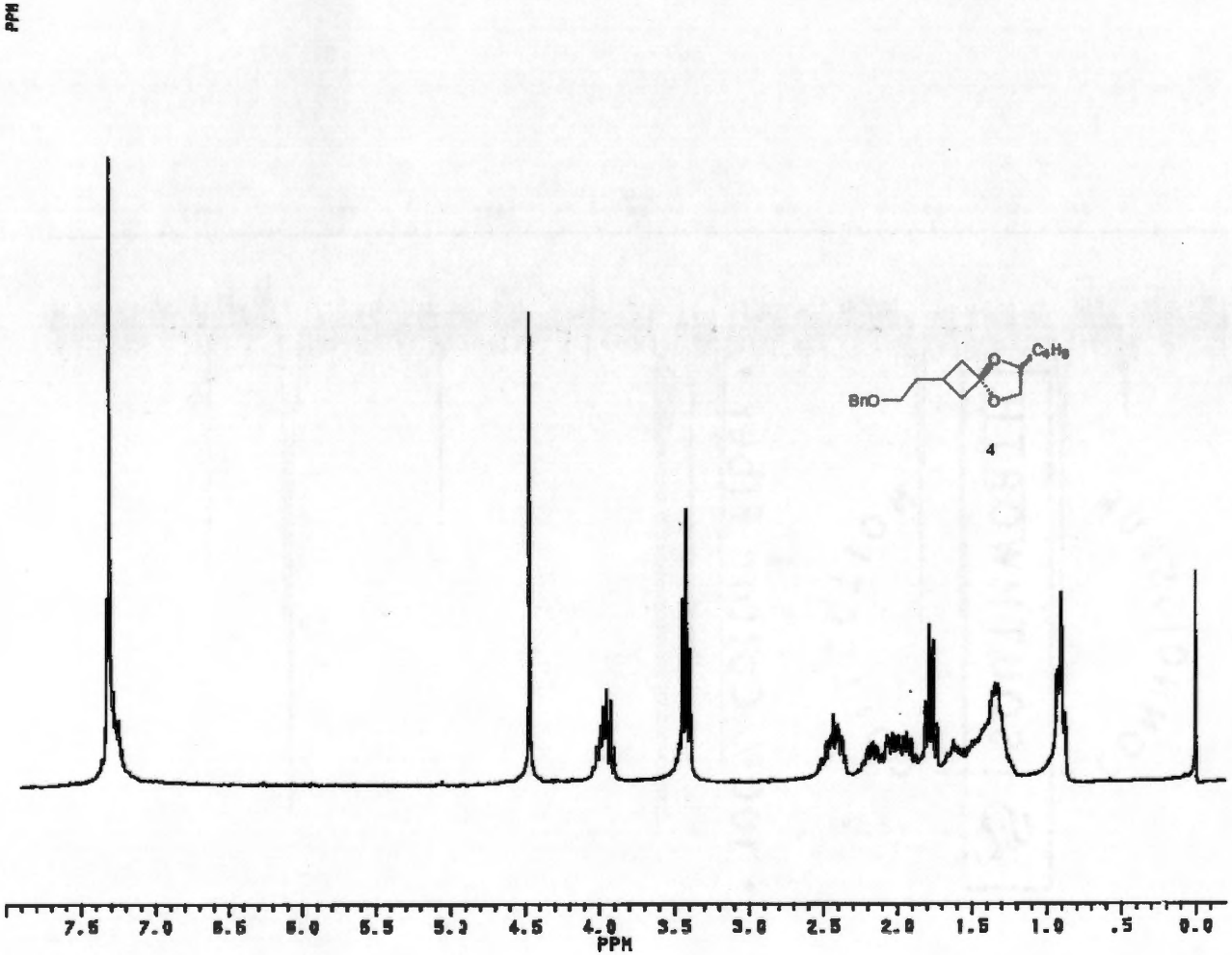
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM


BnO
O
3
140
120
100
80
PPM
40
20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BnO
$C_6H_5$
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O
4
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7.0
6.5
6.0
5.5
5.0
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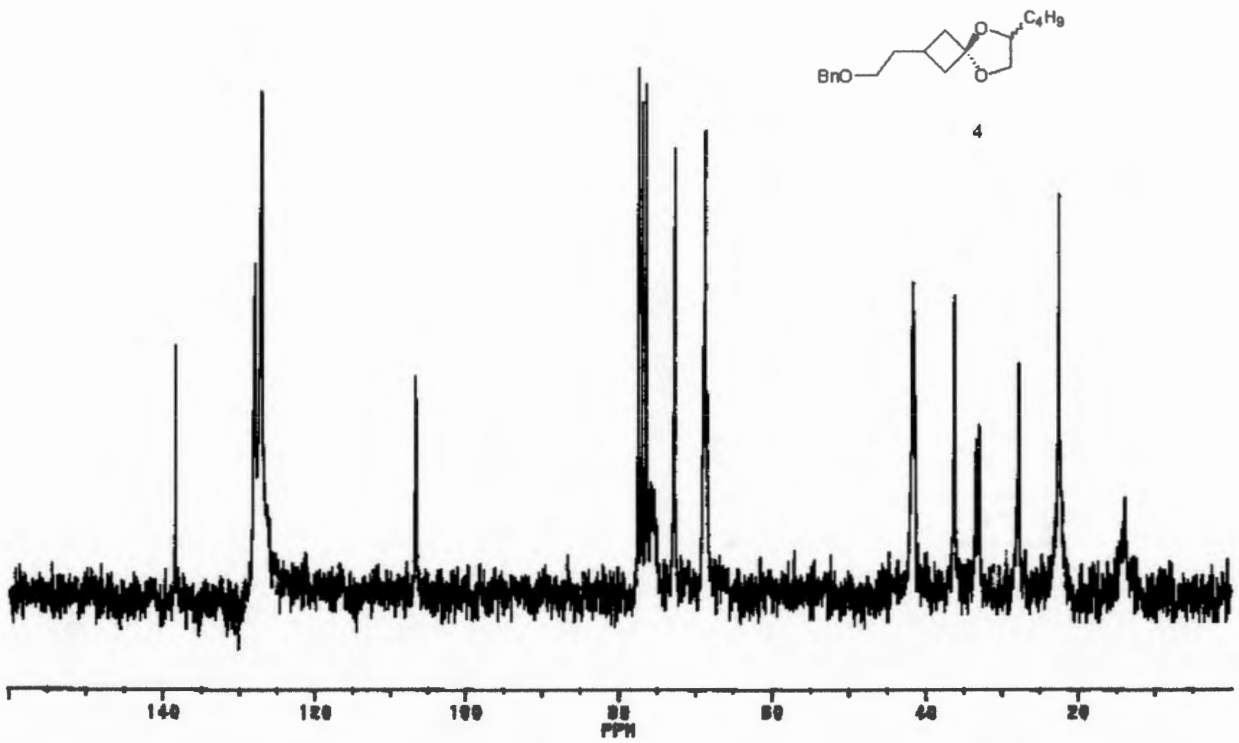
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM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120
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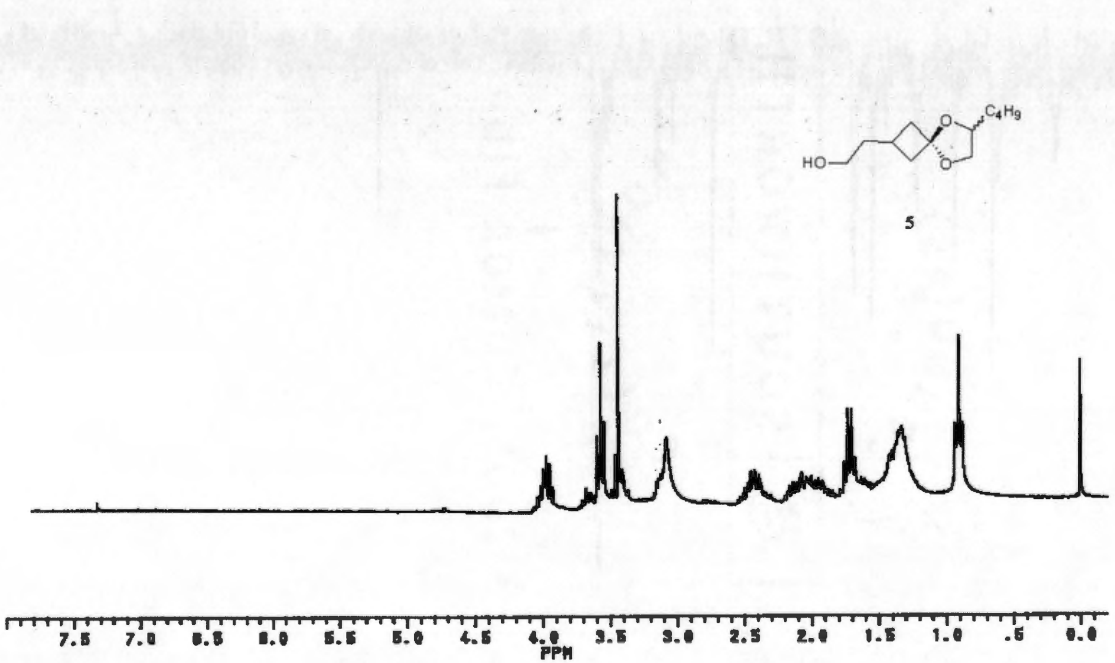
80
60
40
20
PPM


HO
O
O
$C_4H_9$
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7.5
7.0
6.5
6.0
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5.0
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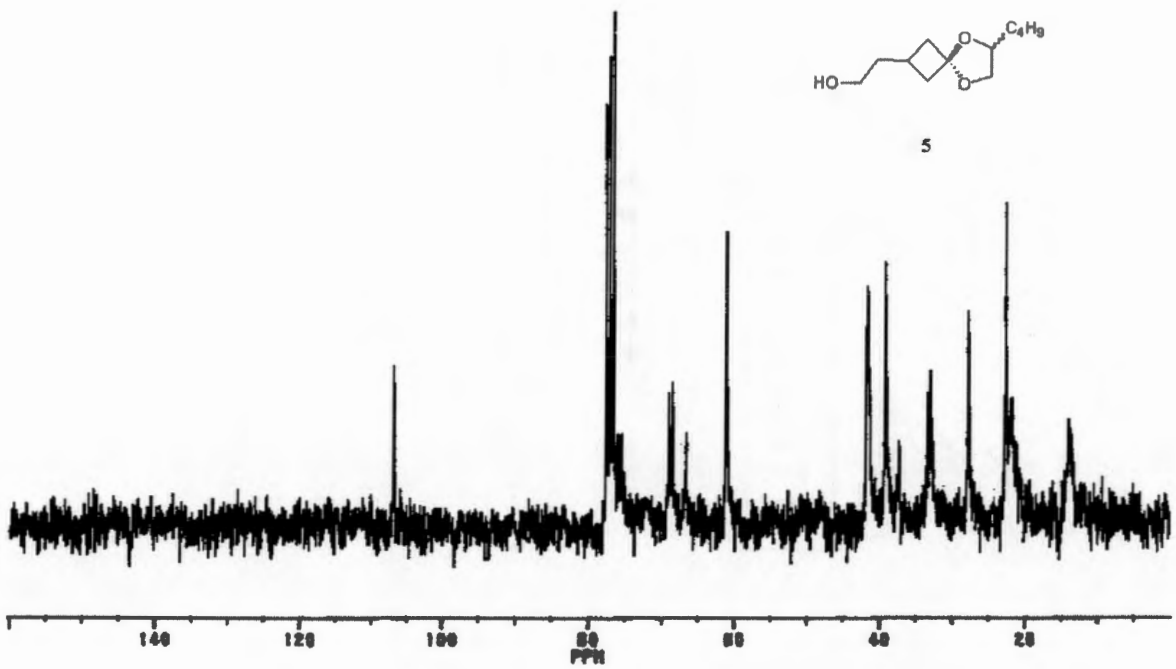
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM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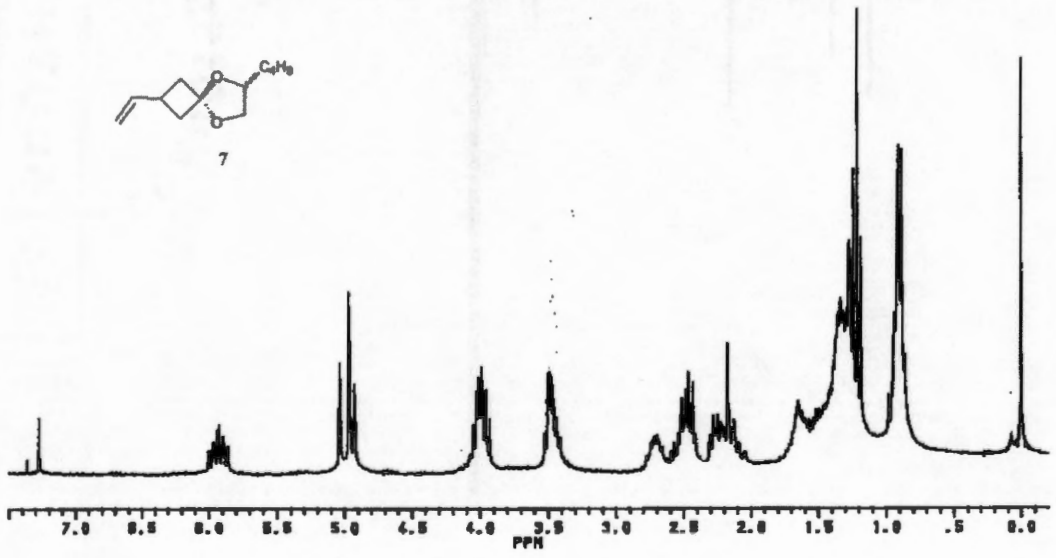
140
120
100
80
60
40
20
PPM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4.0
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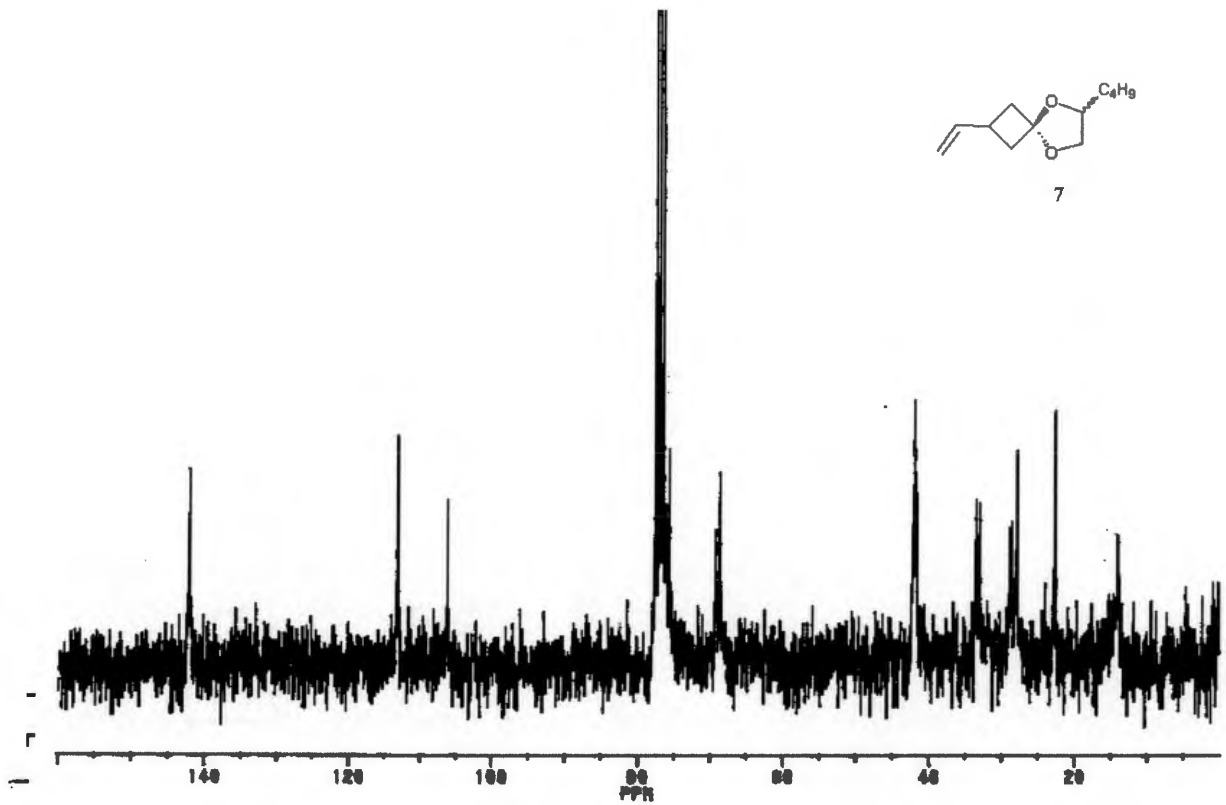
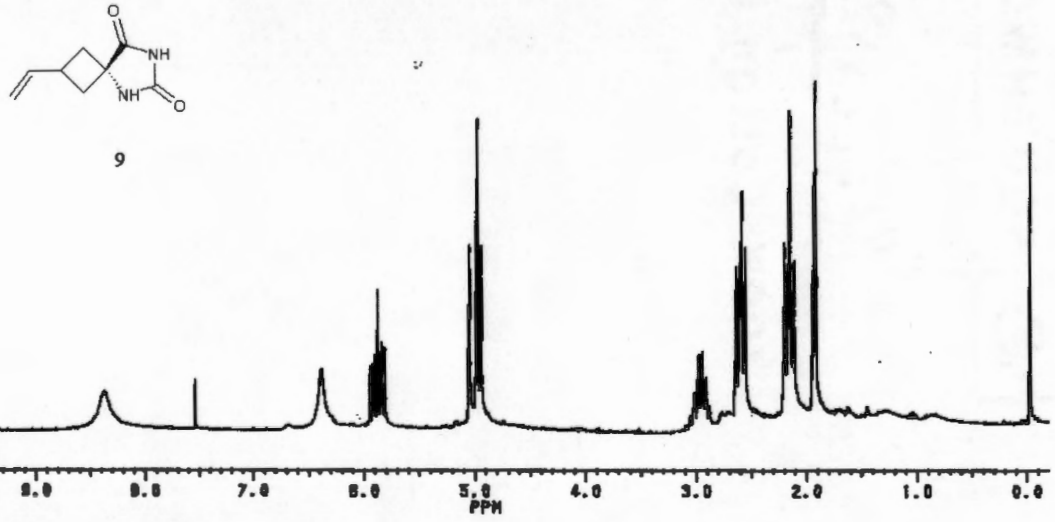
2.0
1.5
1.0
.5
0.0
PPM




7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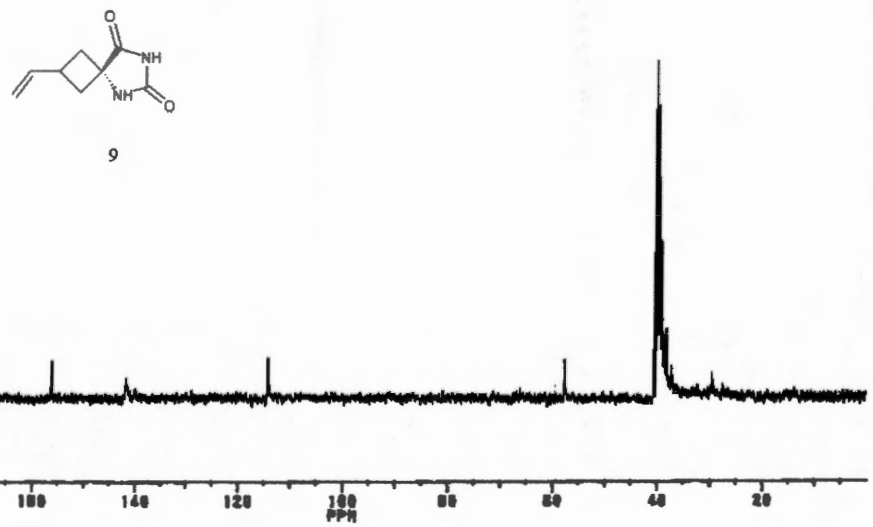
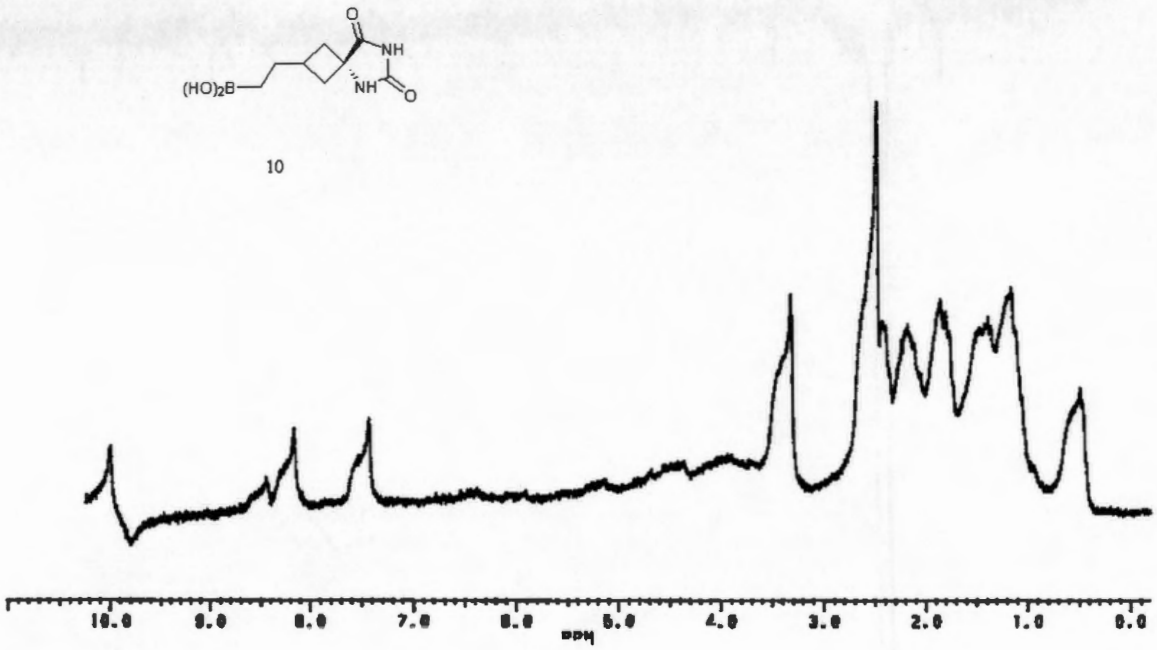
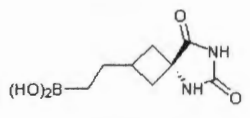
5.0
PPM
4.0
3.0
2.0
1.0
0.0

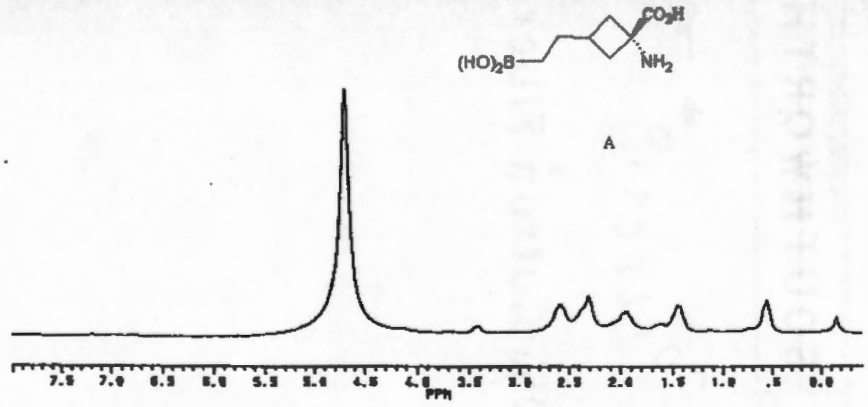


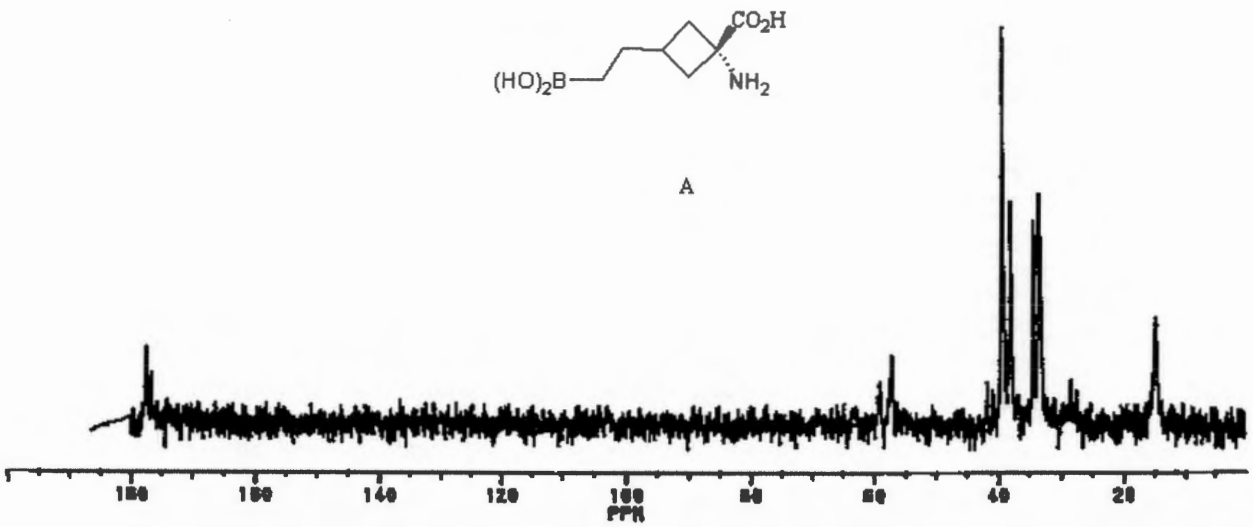

9


O
NH
(HO)2B
NH
O
10
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm

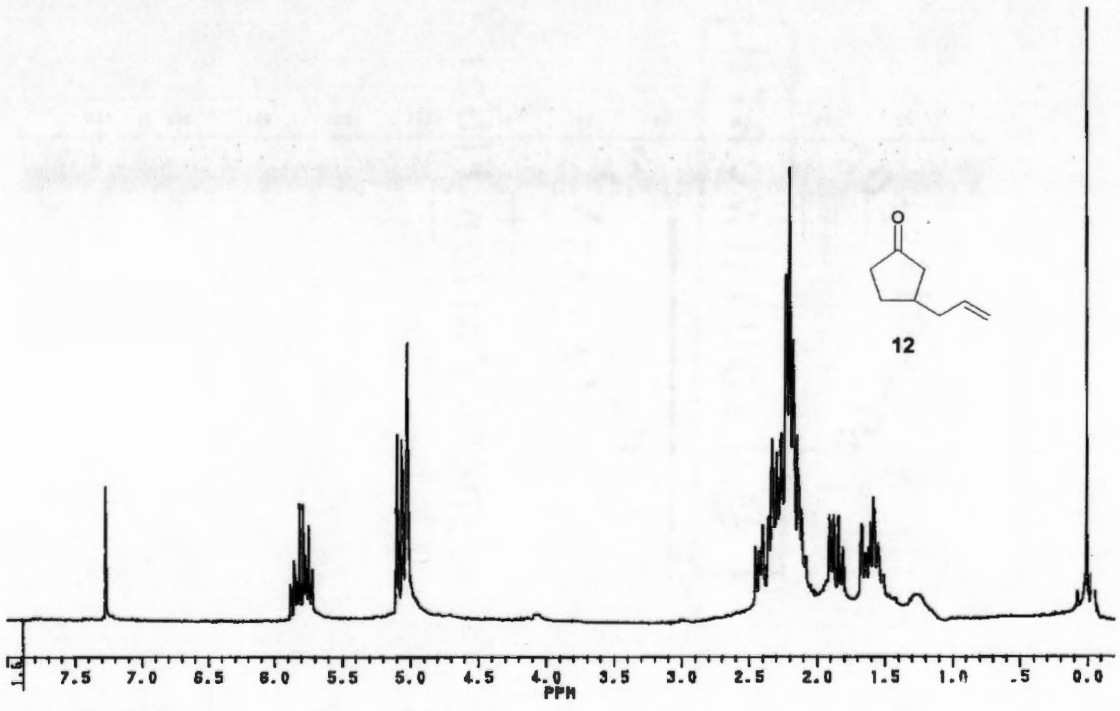



10

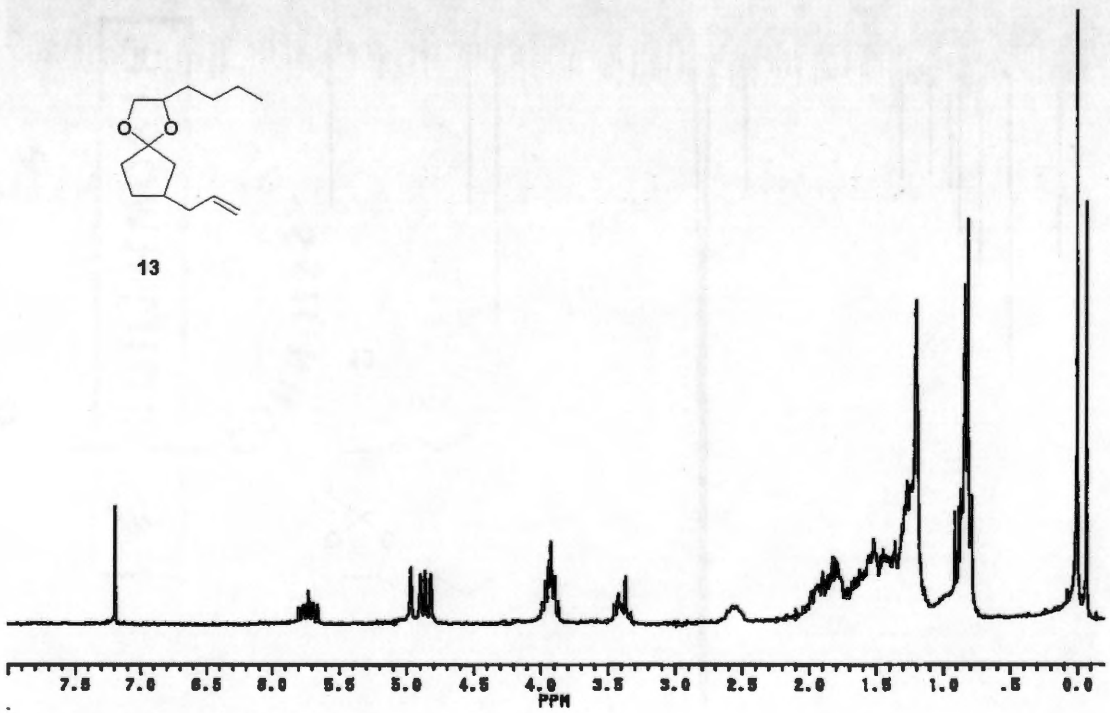

CO2H
(HO)2B
NH2
A
PPM

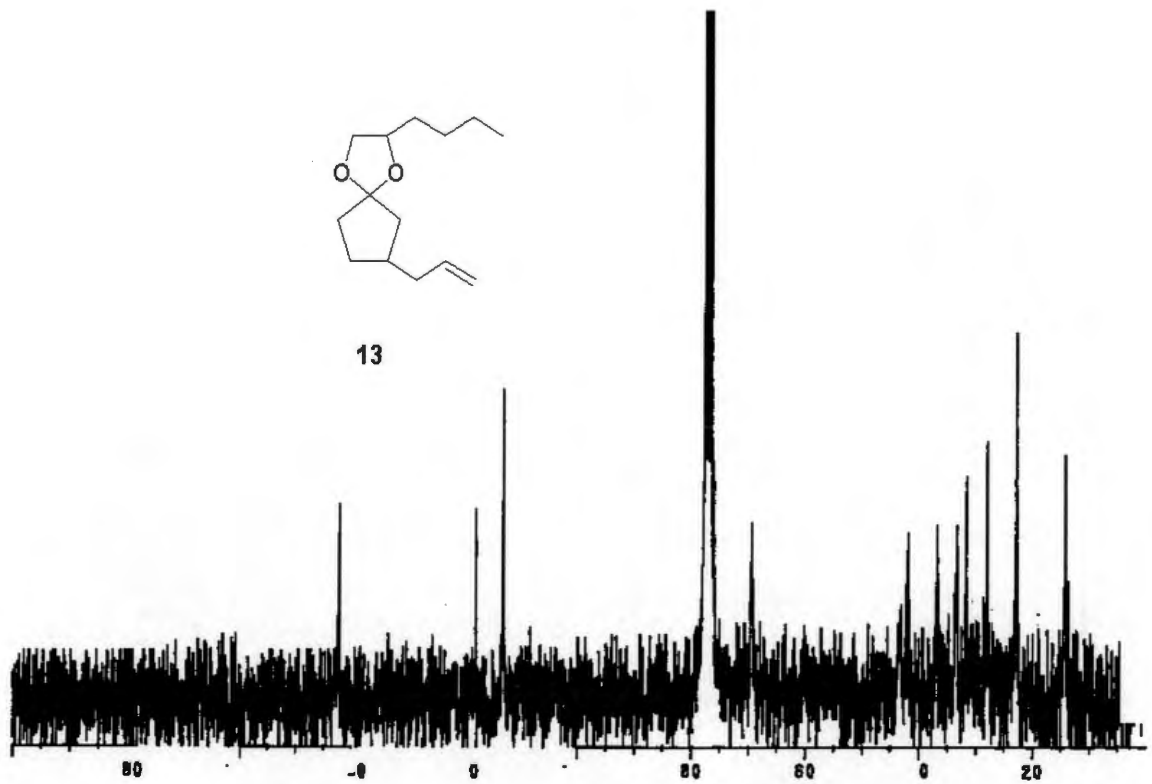


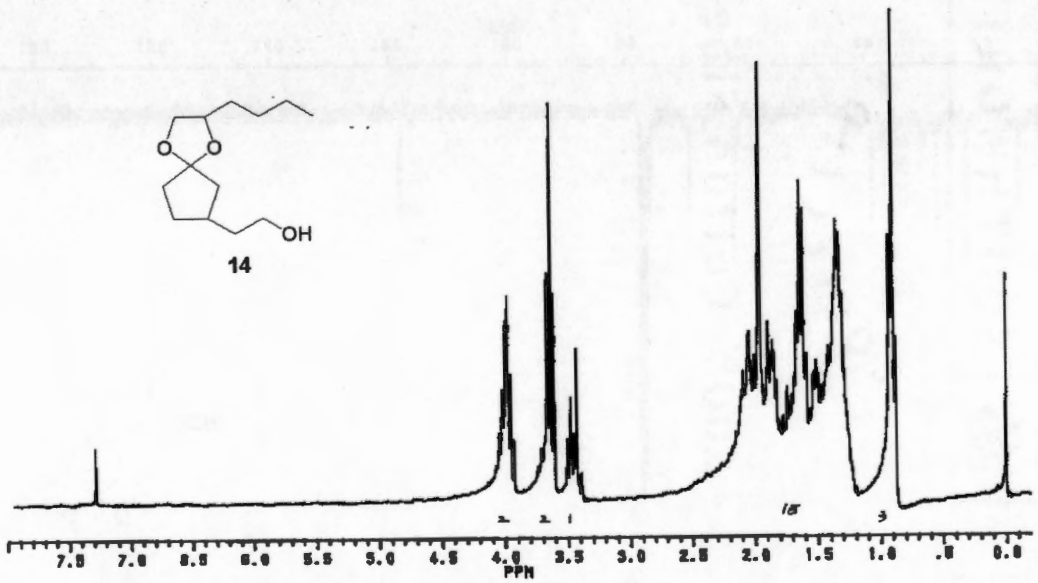

A


12
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

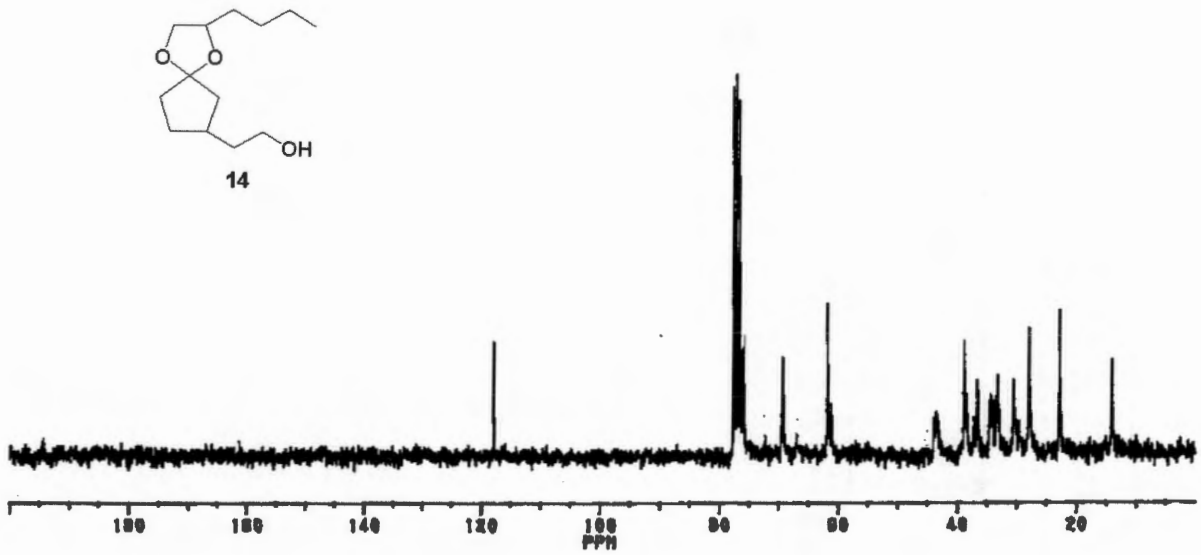
O
12
220
200
180
160
140
120
100
80
60
40
20
PPM

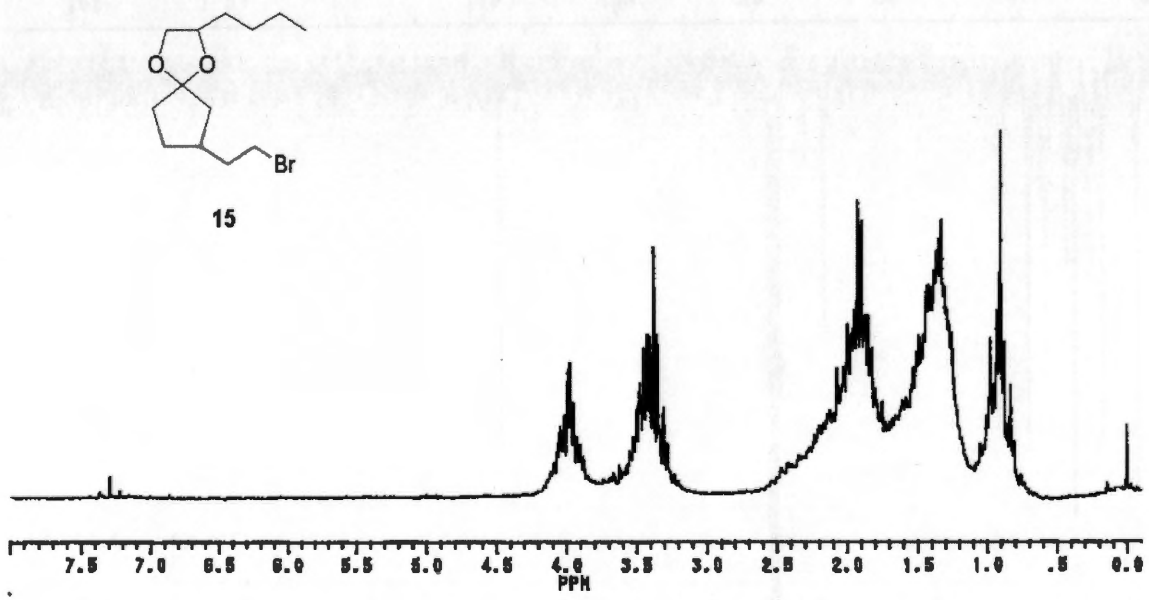

13
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


O
O
13
80
-0
0
80
60
0
20

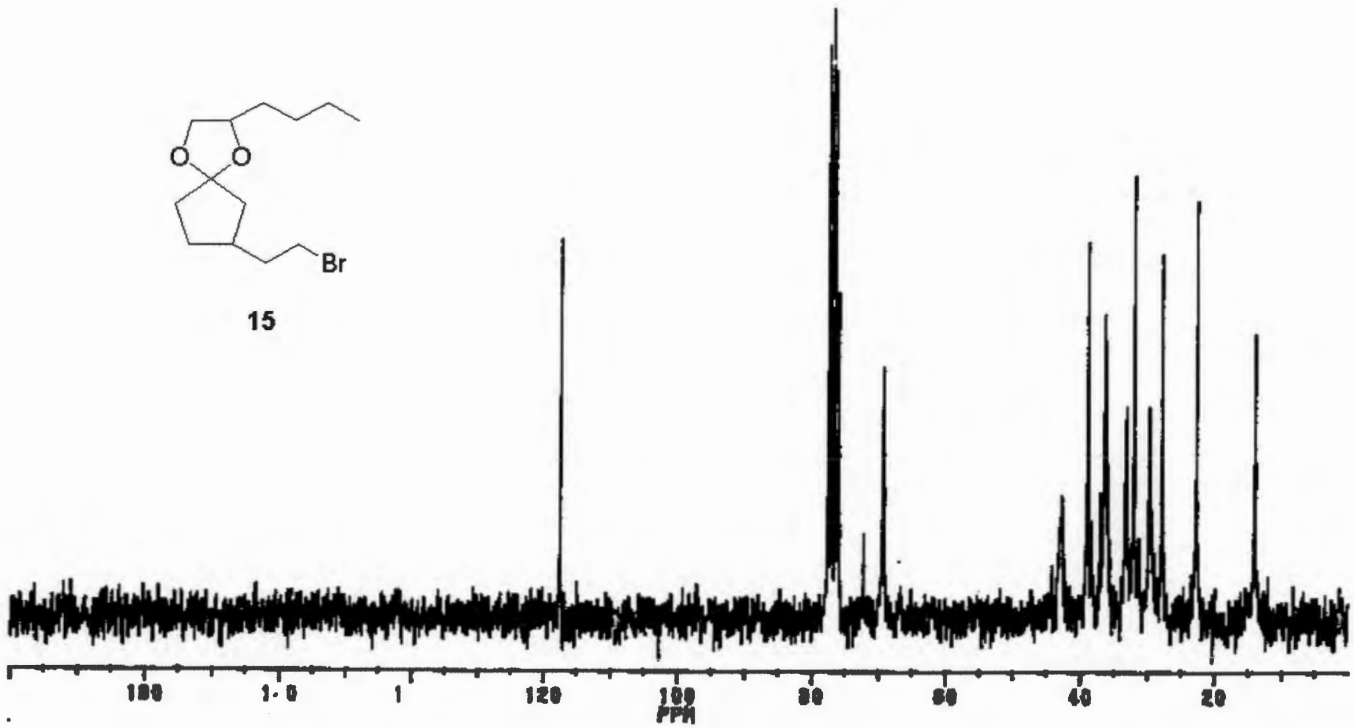


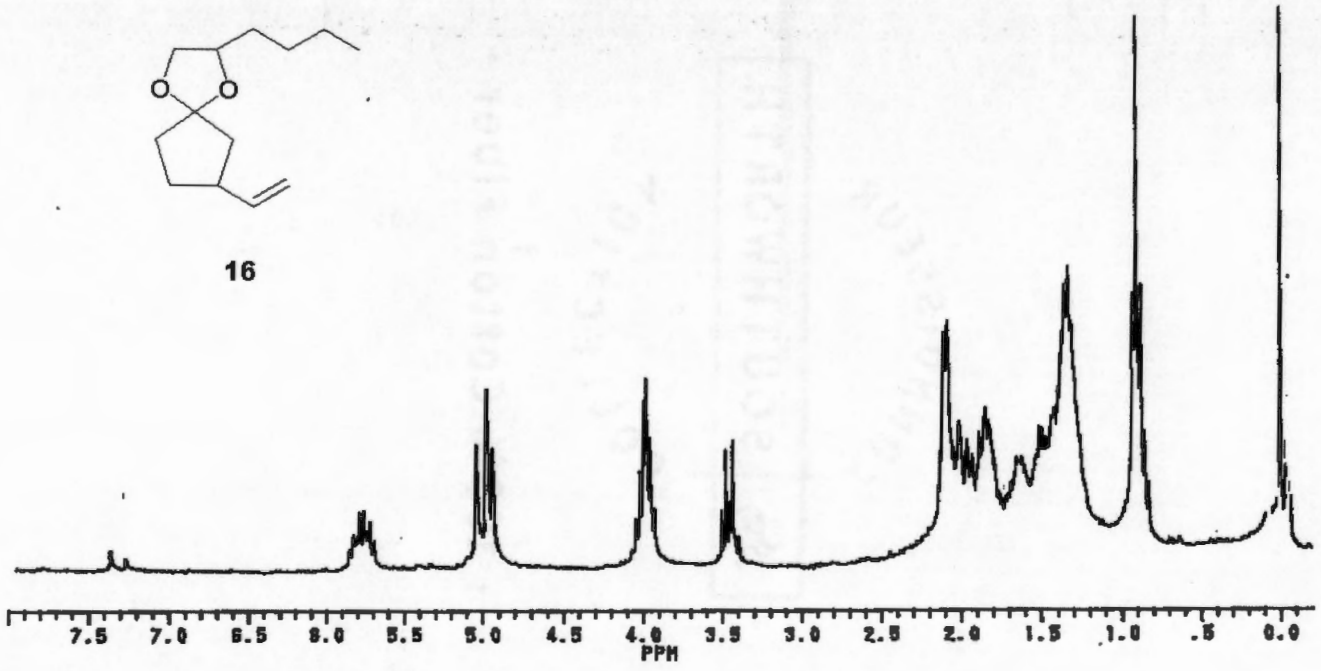

14


O
O
OH
14
180
160
140
120
100
PPM
80
60
40
20

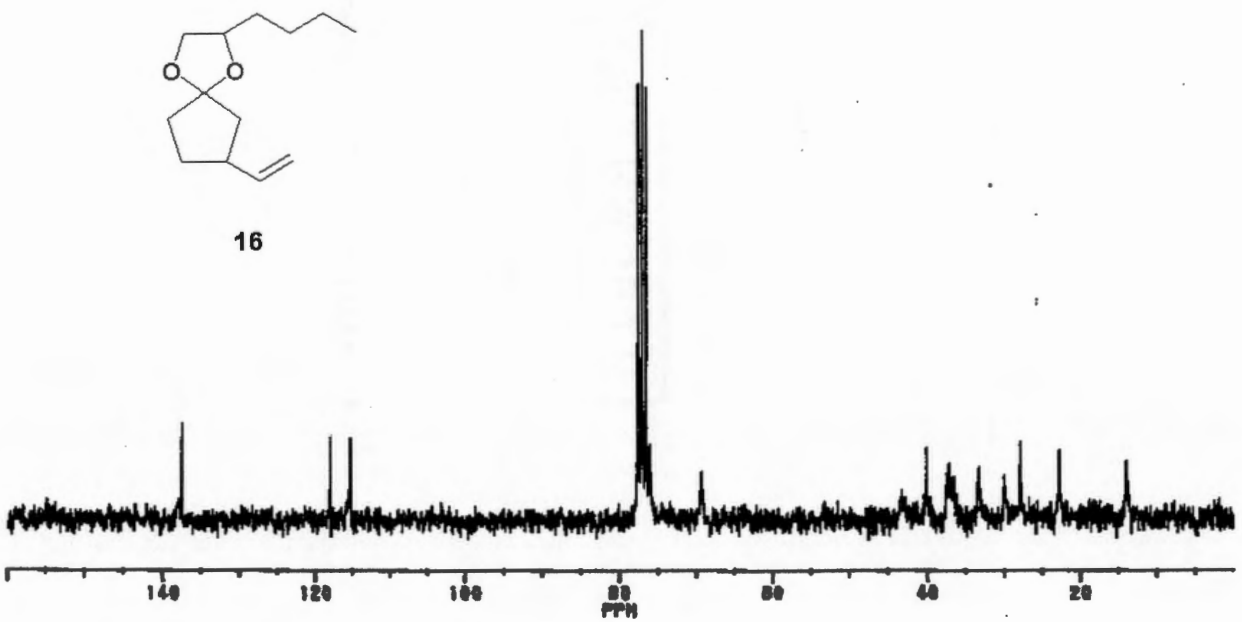


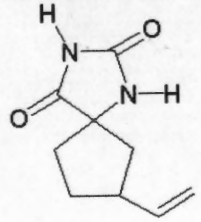

15


O
O
Br
15
160
140
120
100
PPM
80
60
40
20




16


16
140
120
100
80
60
40
20
PPM

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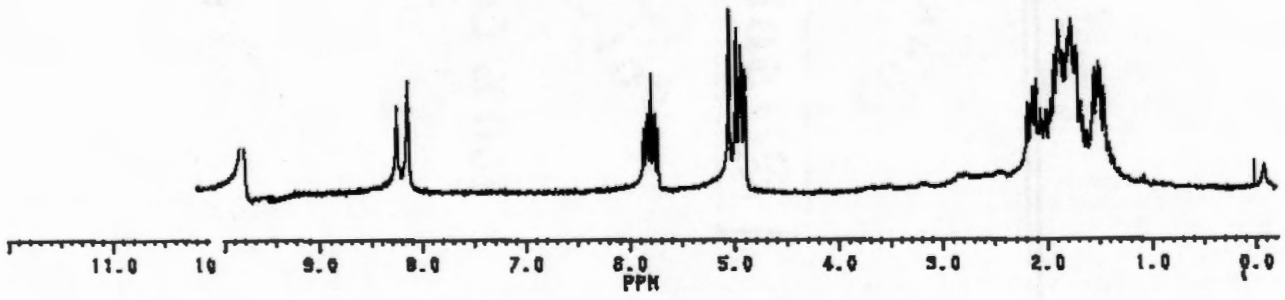
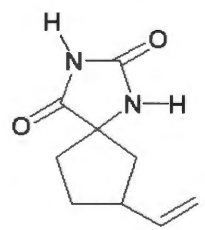
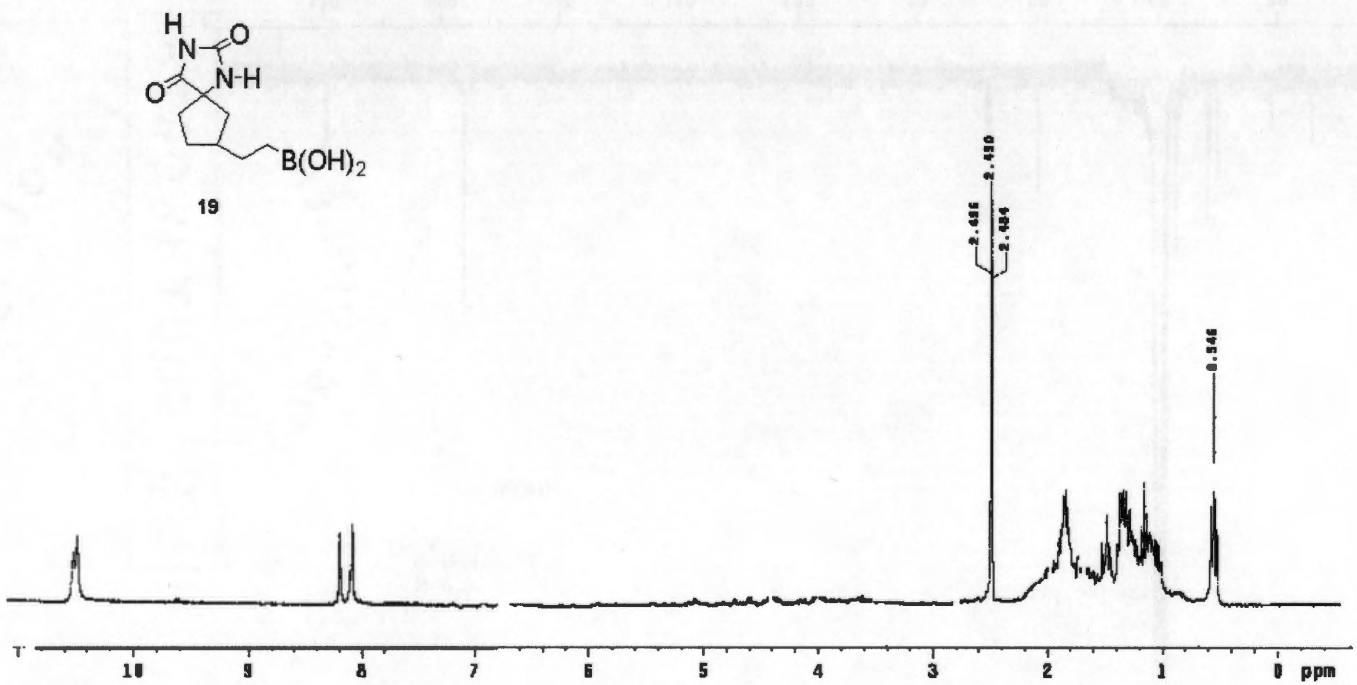
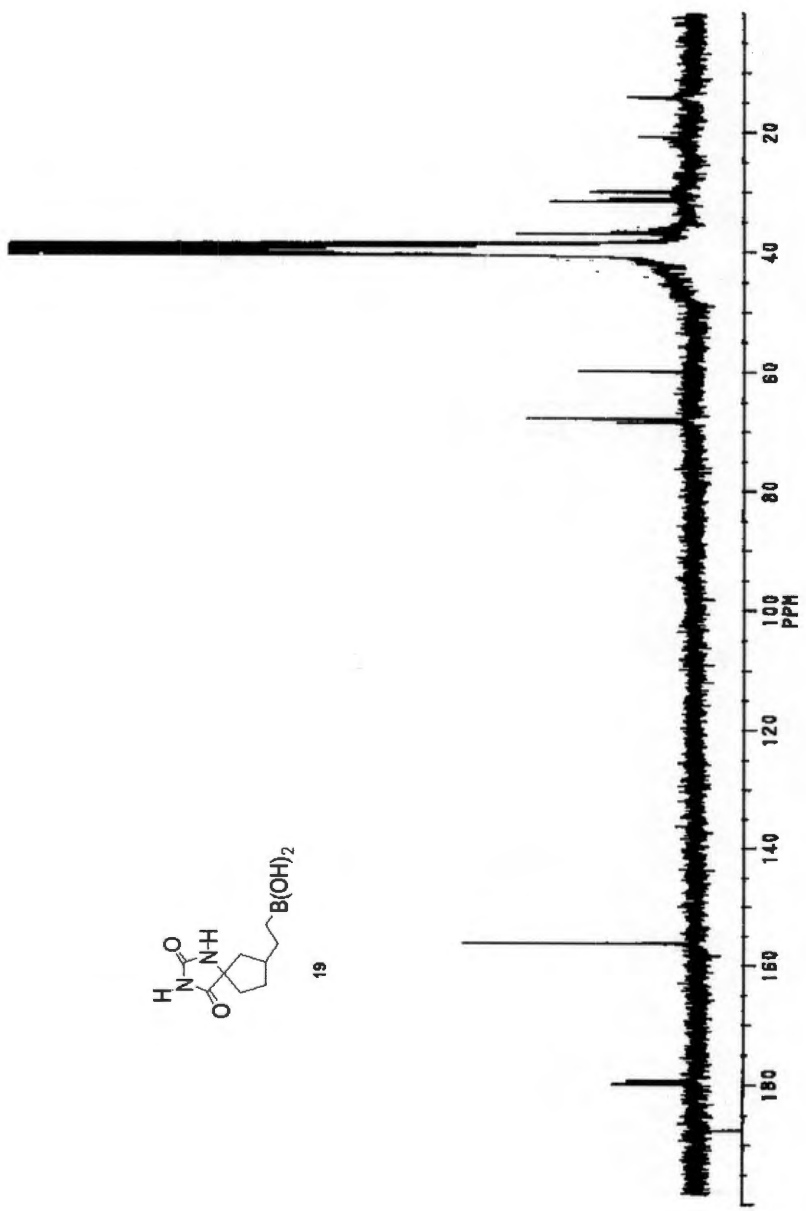
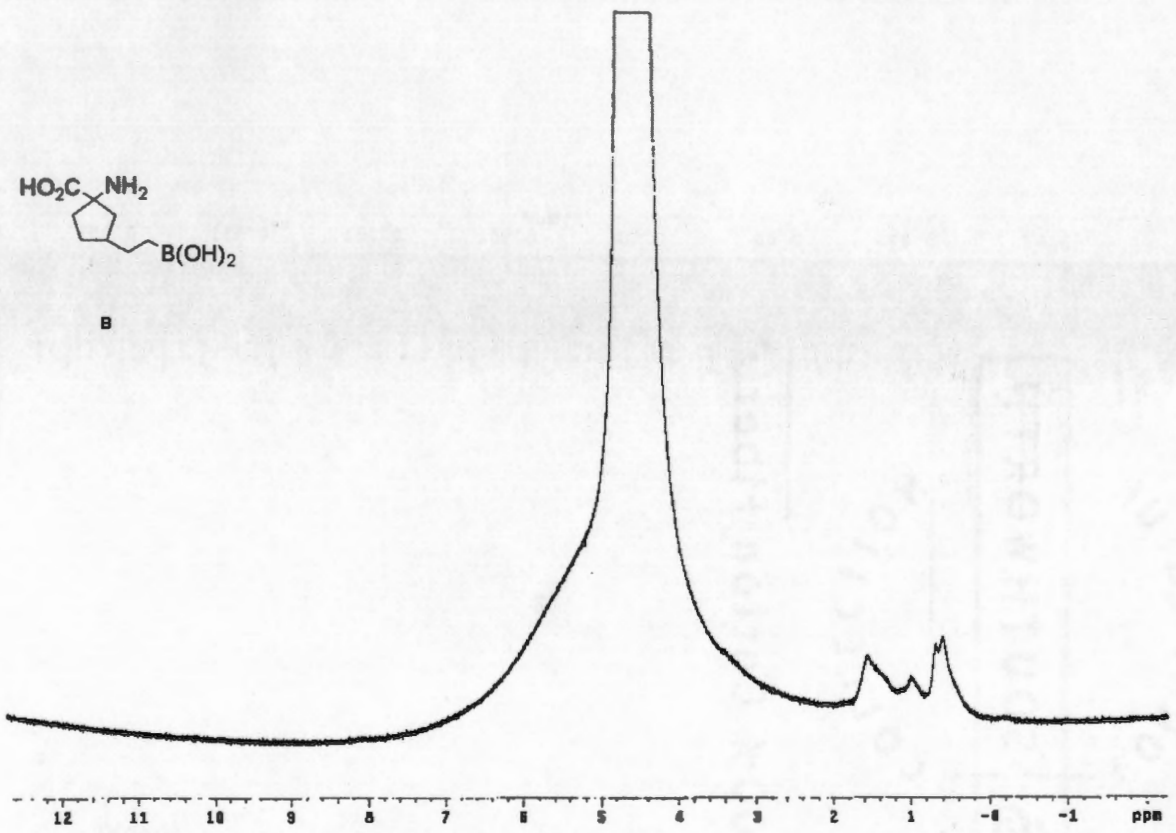


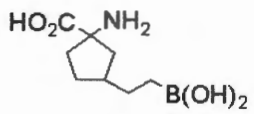



18

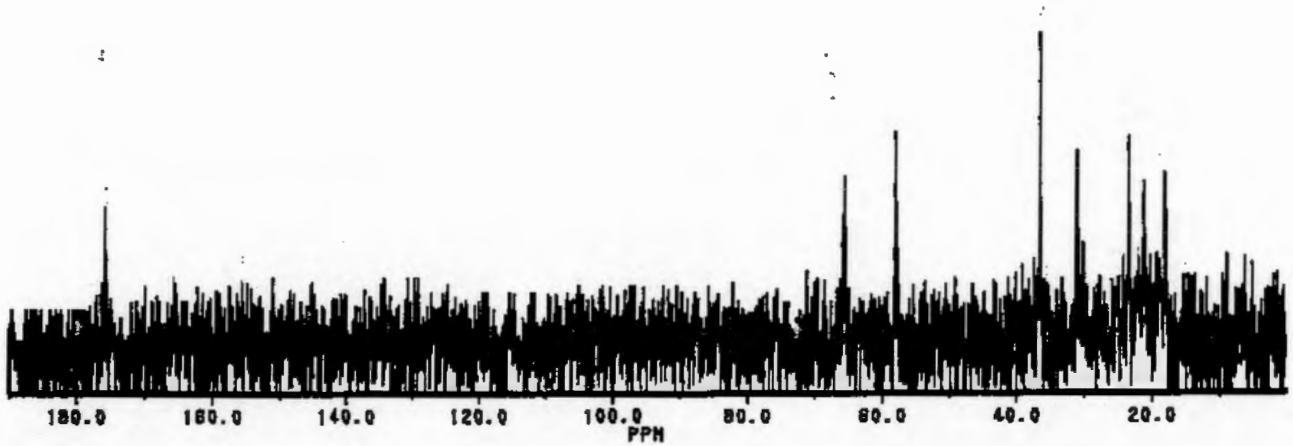

H
N
O
O
N-H
B(OH)2
19
2.486
2.480
2.464
0.846
10
9
8
7
6
5
4
3
2
1
0
ppm

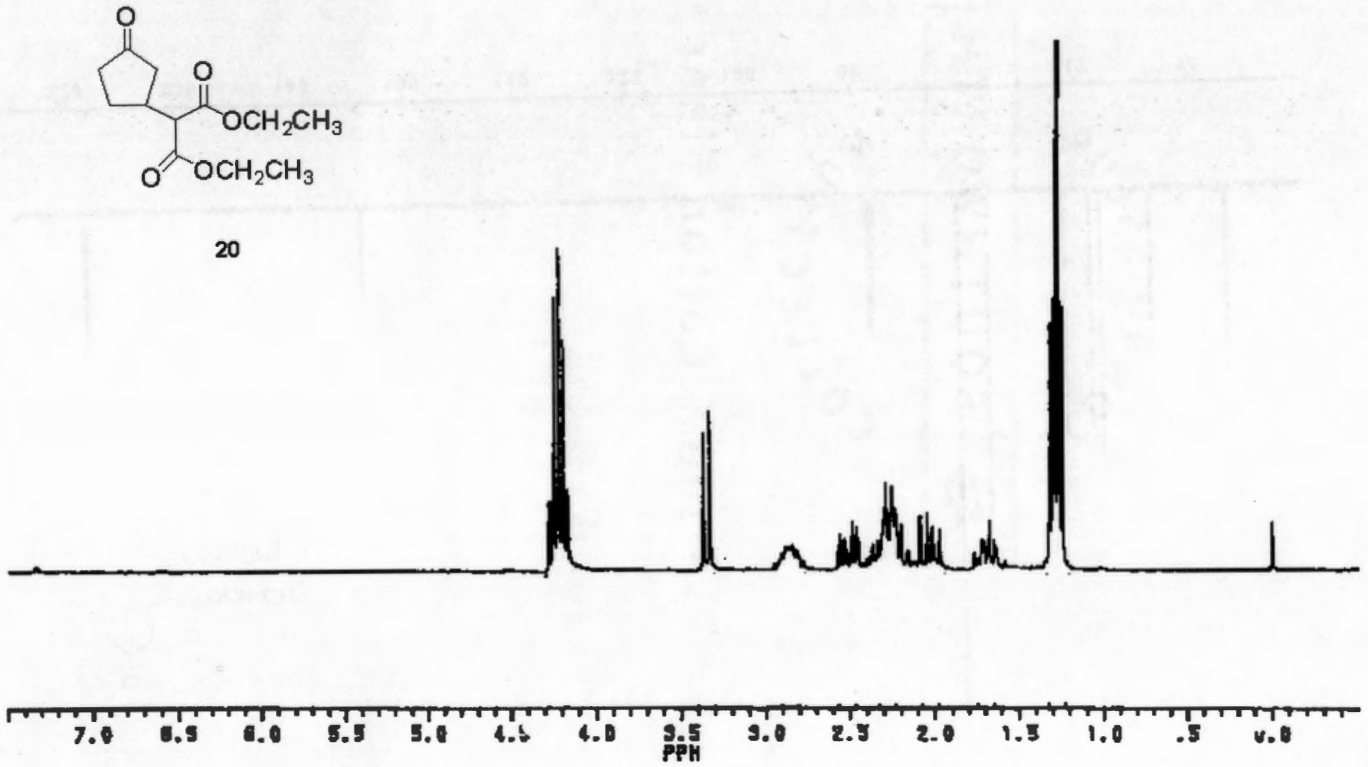

B(OH)2
19
20
40
60
80
100
120
140
160
180
PPM


HO2C
NH2
B(OH)2
B
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm




B



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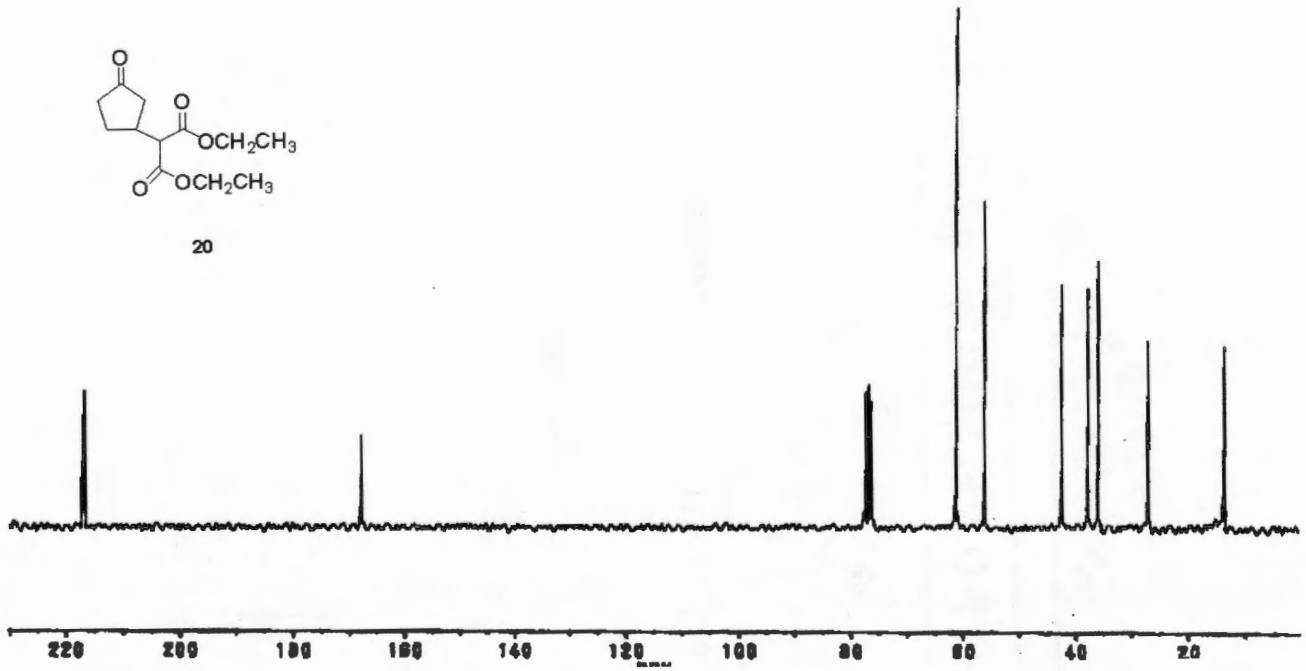


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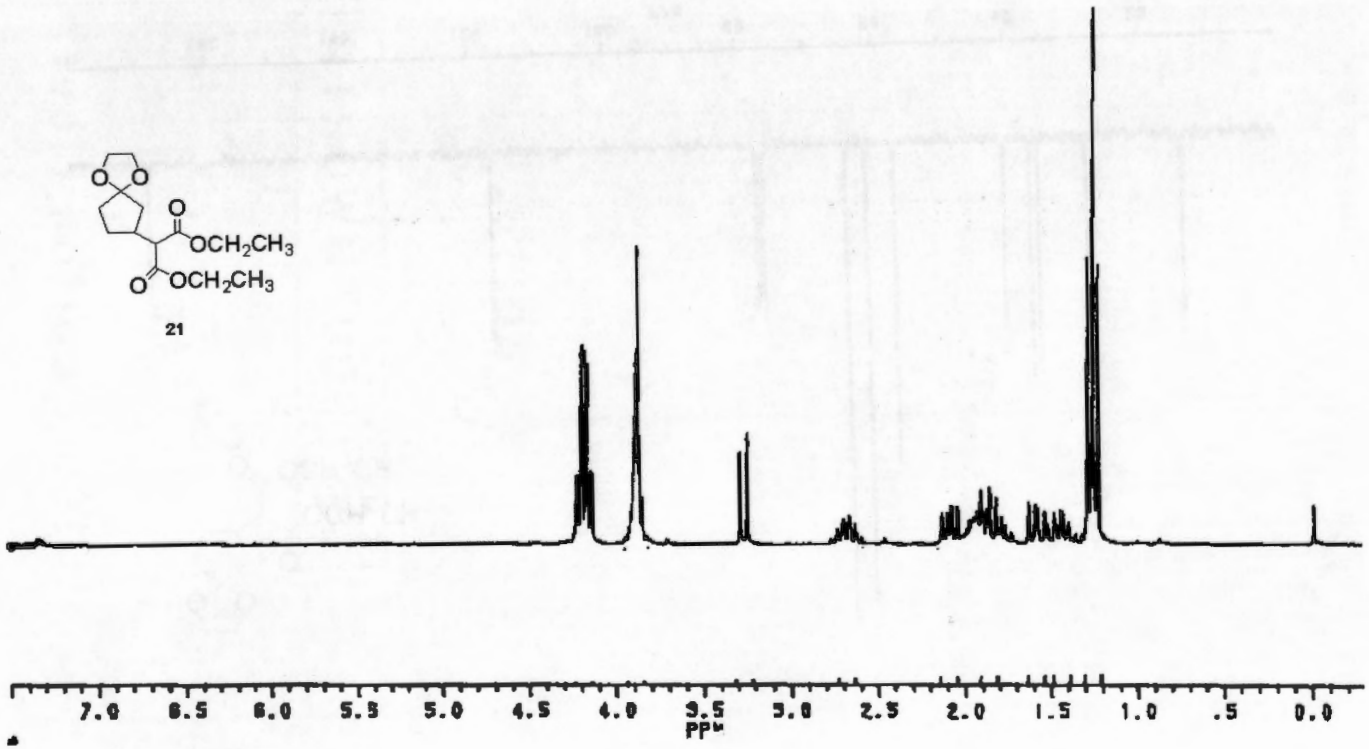


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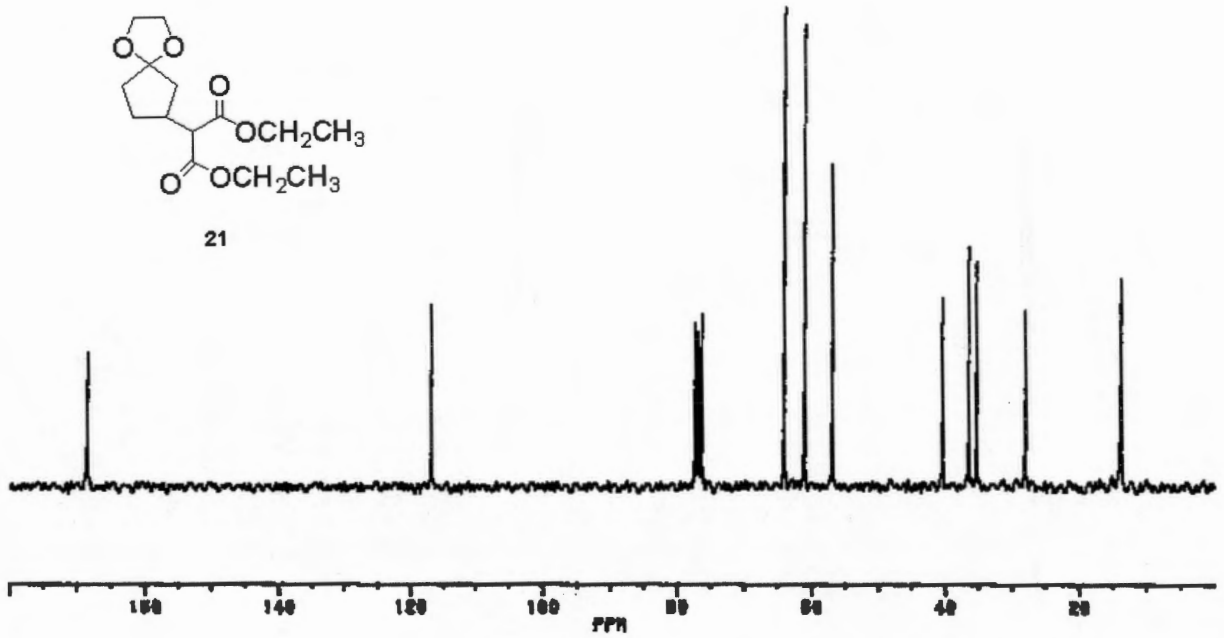
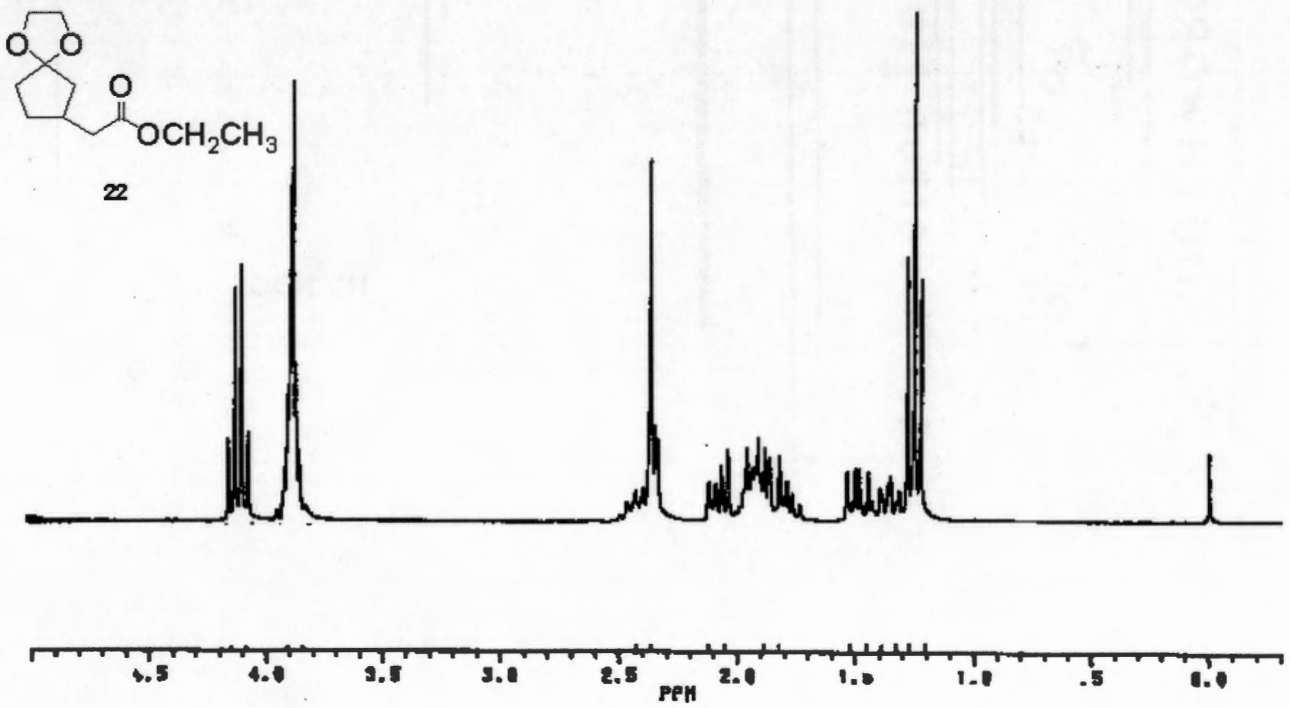
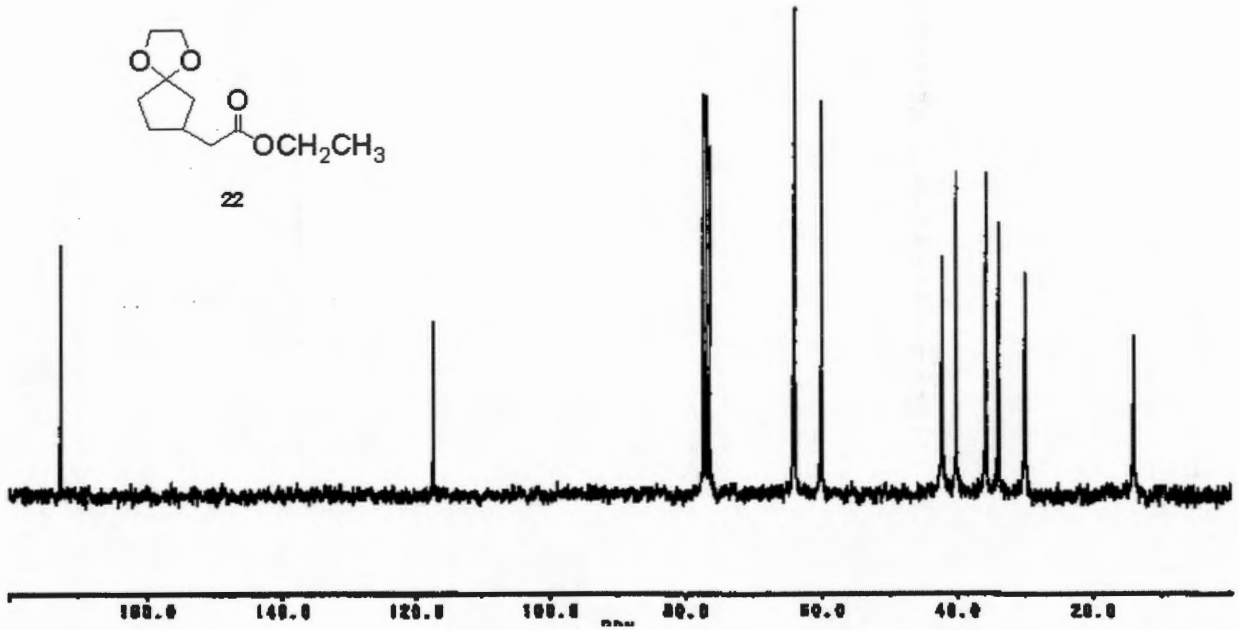
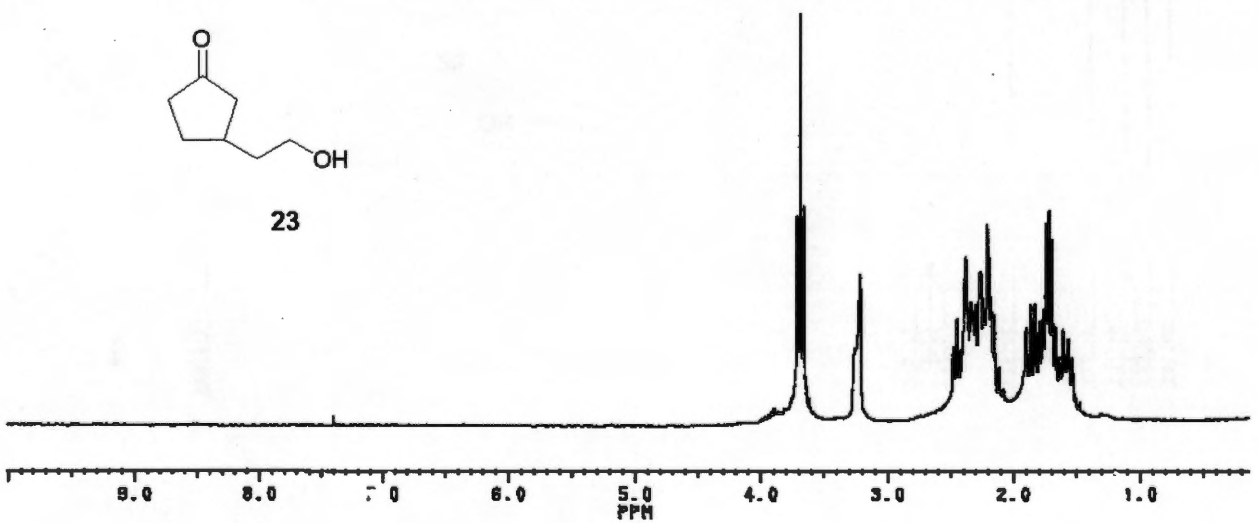

O
O
O
OCH2CH3
O
OCH2CH3
21
160
140
120
100
80
60
40
20
PPM

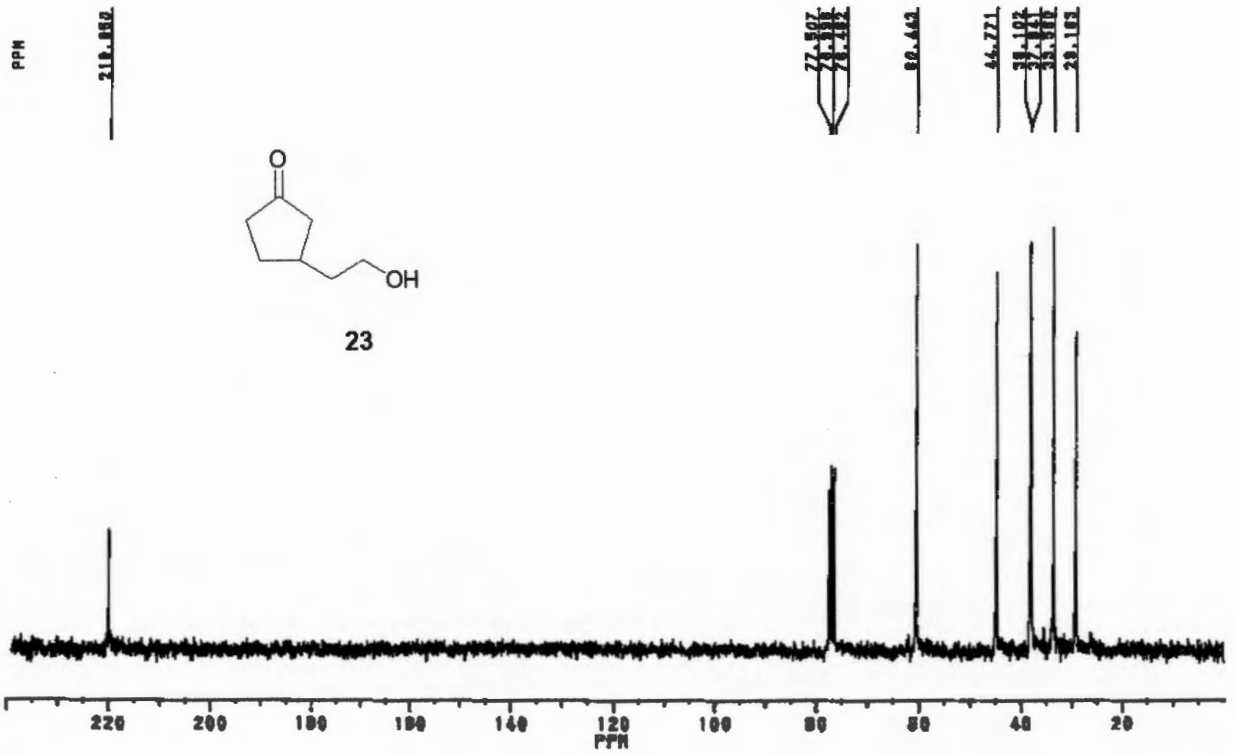

O
O
O
OCH2CH3
22
PPM



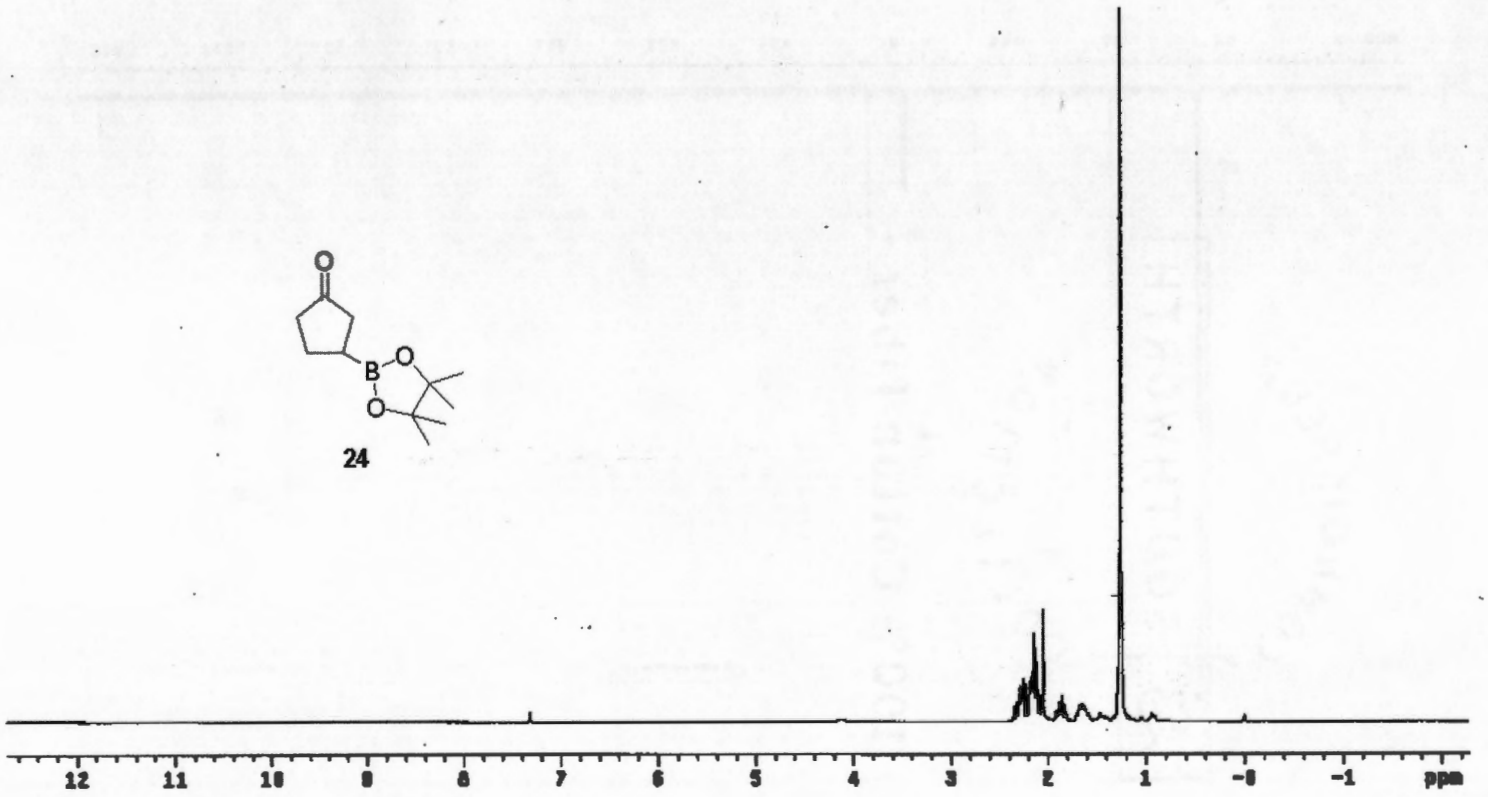

22



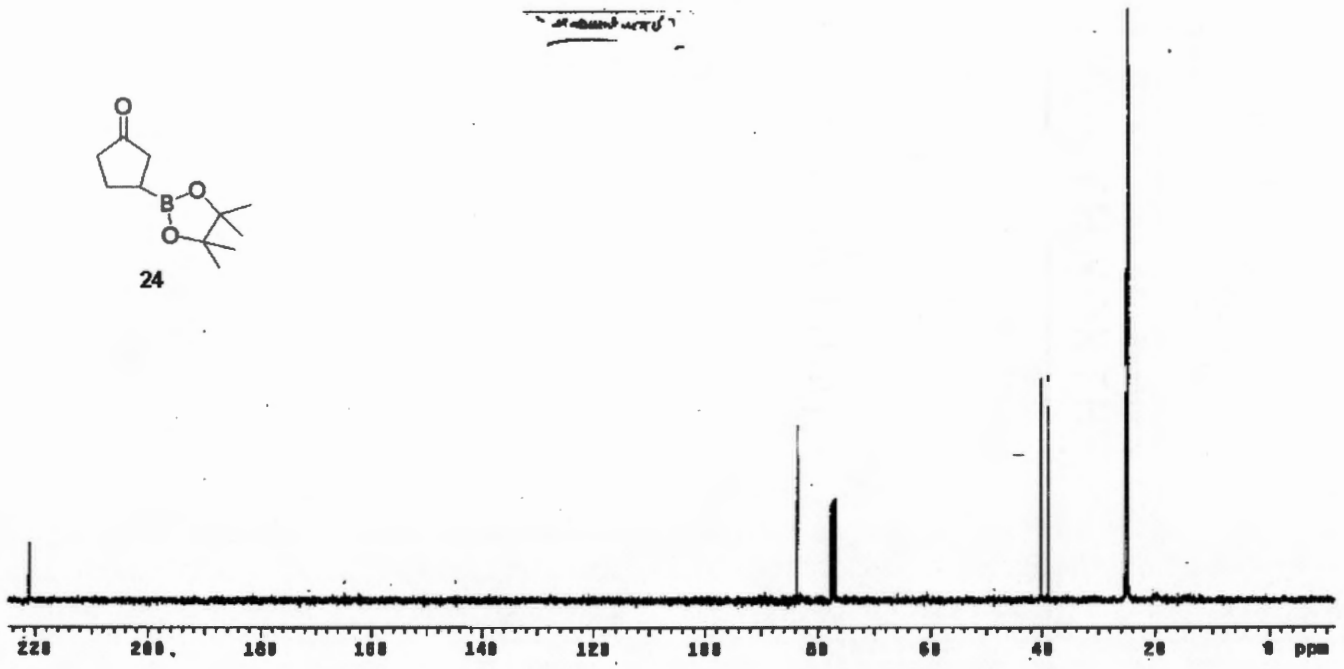

23

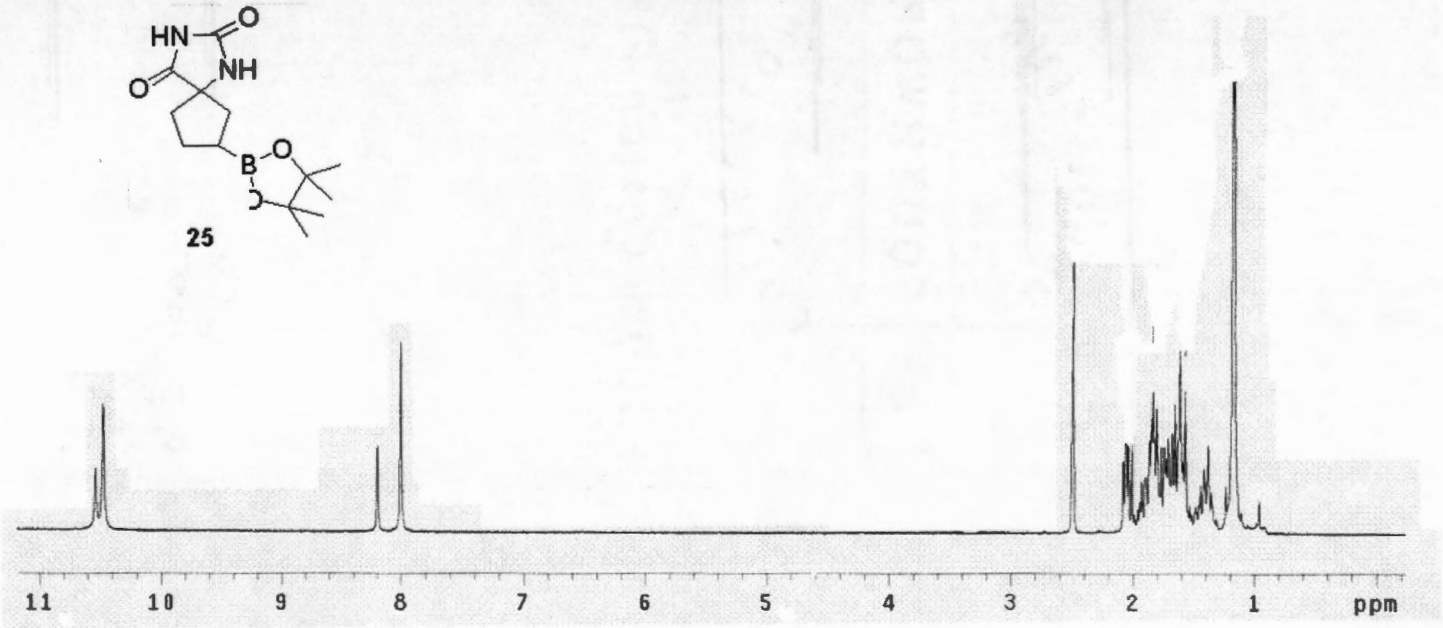



23

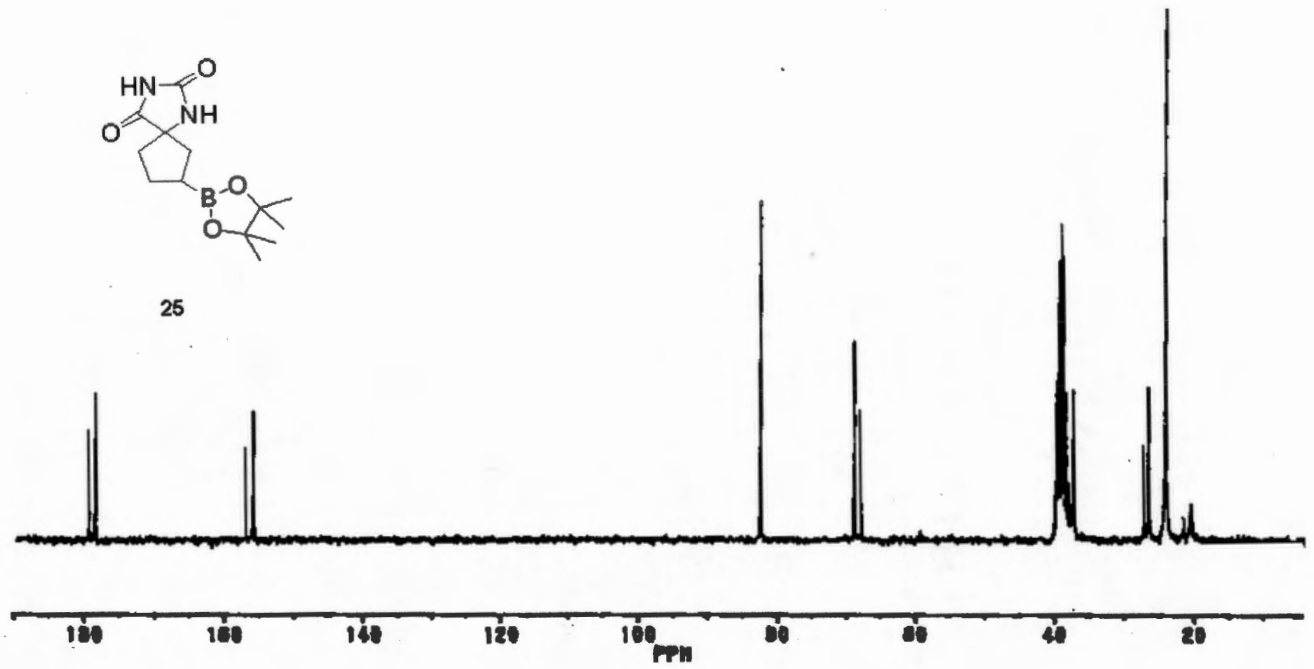


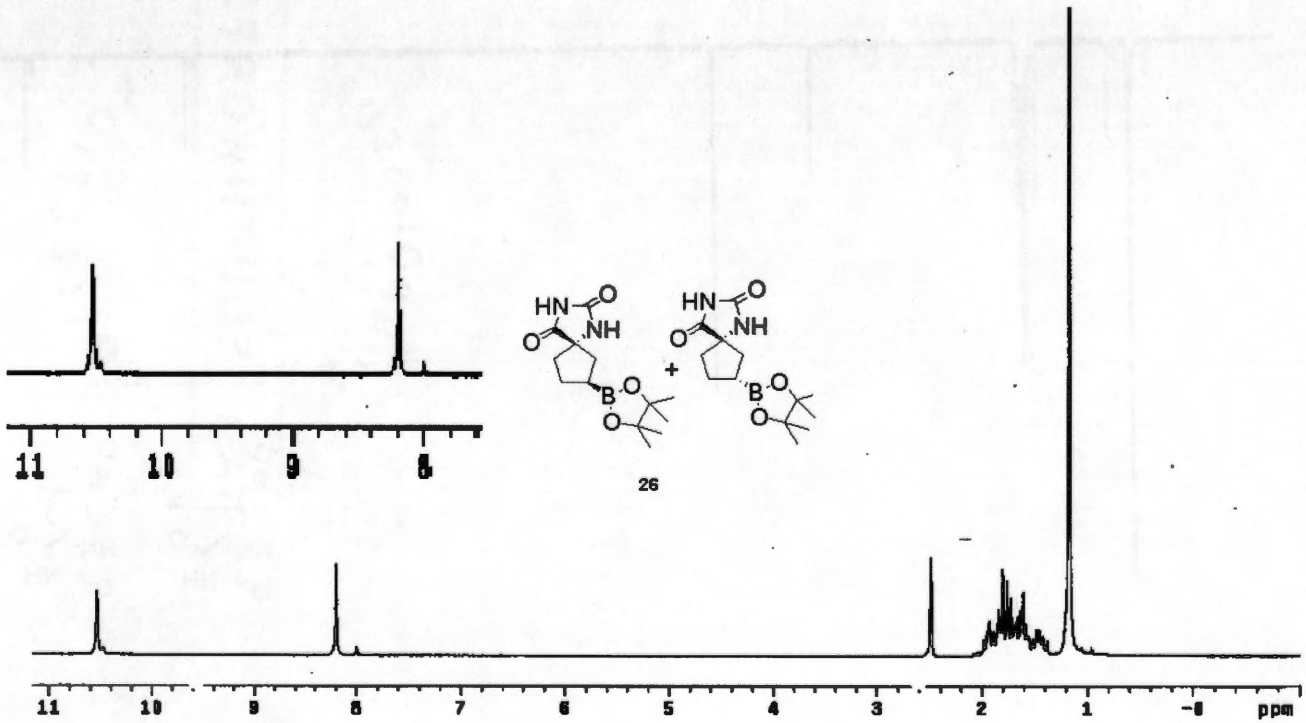

24

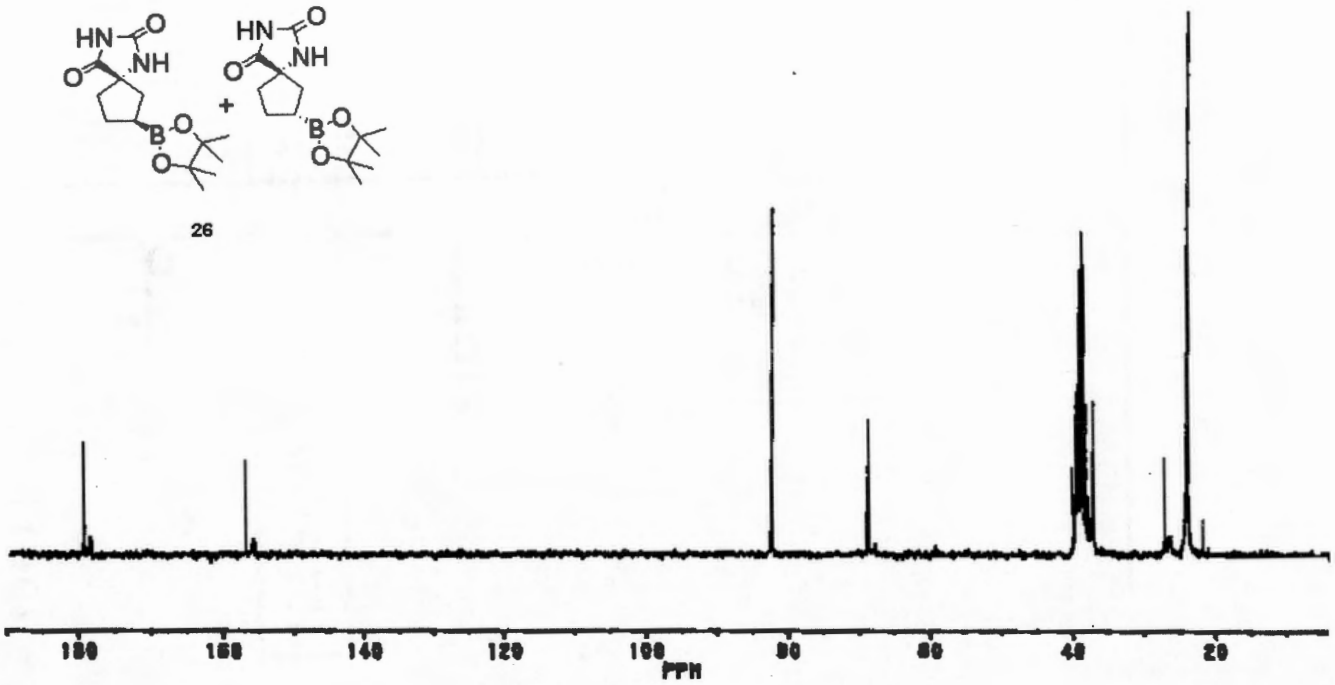

O
B
O
O
24
220
200
180
160
140
120
100
80
60
40
20
0
ppm

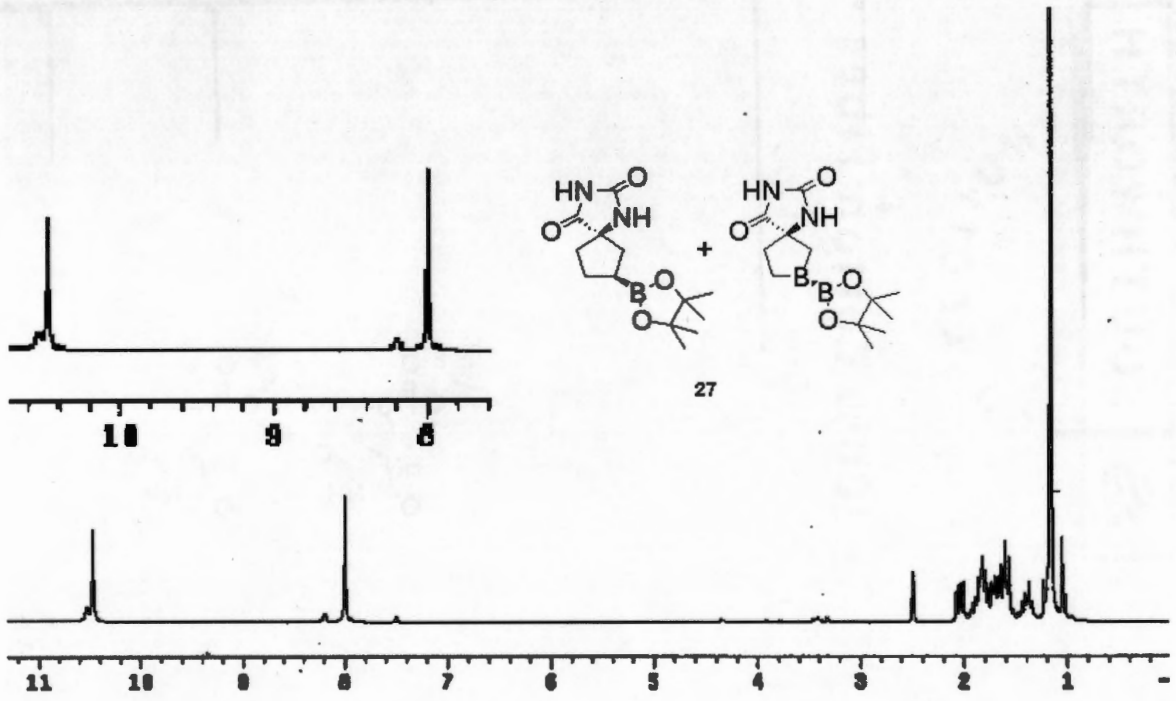


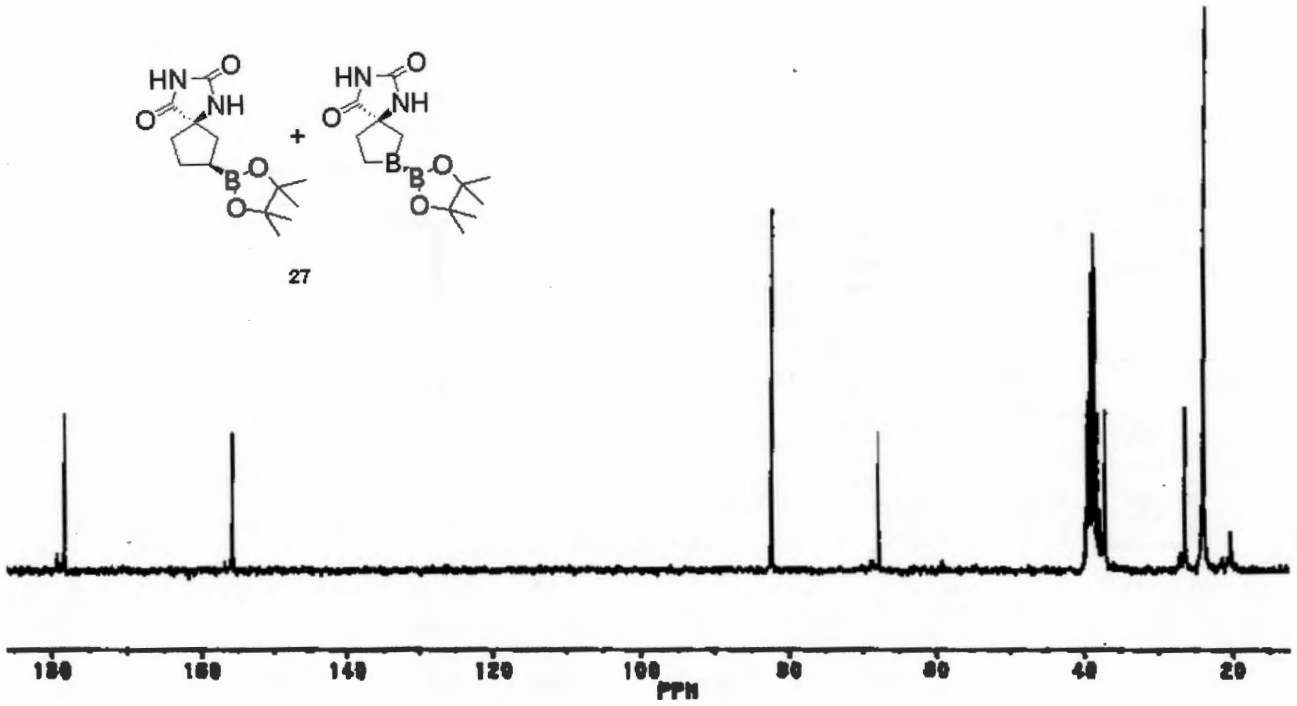

25

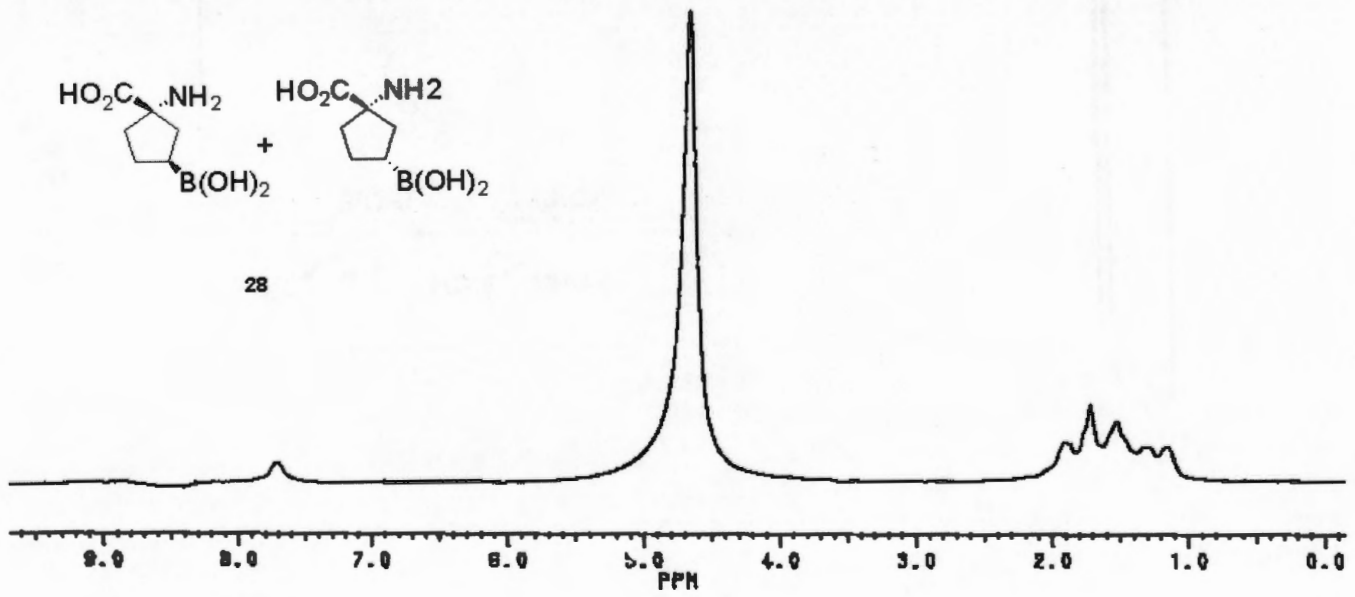

HN
O
NH
O
B
O
O
25
180
160
140
120
100
80
60
40
20
PPM

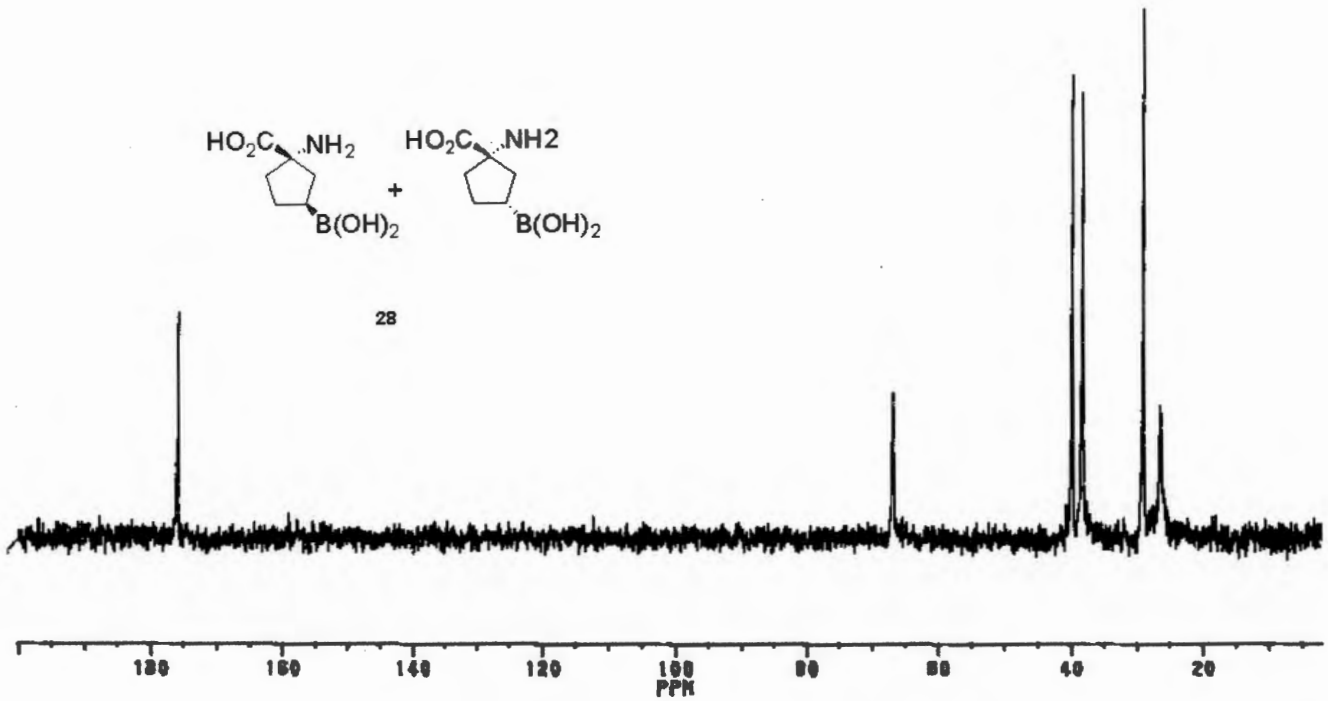

HN
O
NH
O
B
O
O
+
26
11
10
9
8
7
6
5
4
3
2
1
-0
ppm

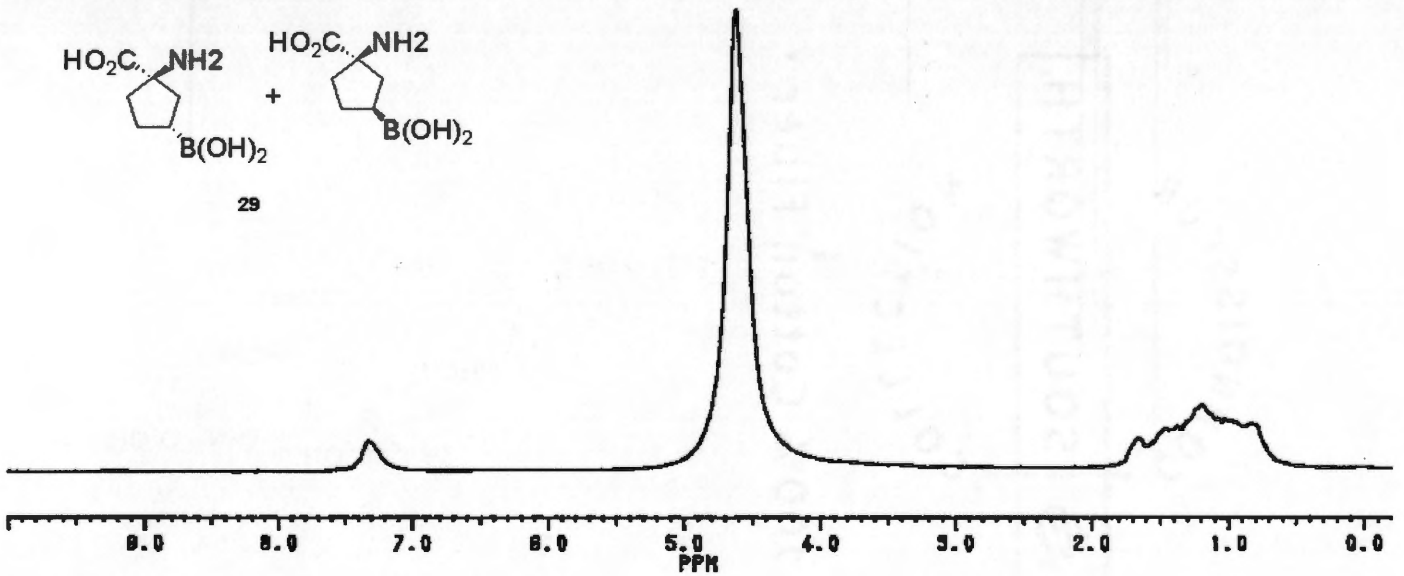

HN
O
NH
O
B
O
O
+
HN
O
NH
O
B
O
O
26
180
160
140
120
100
80
60
40
20
PPM

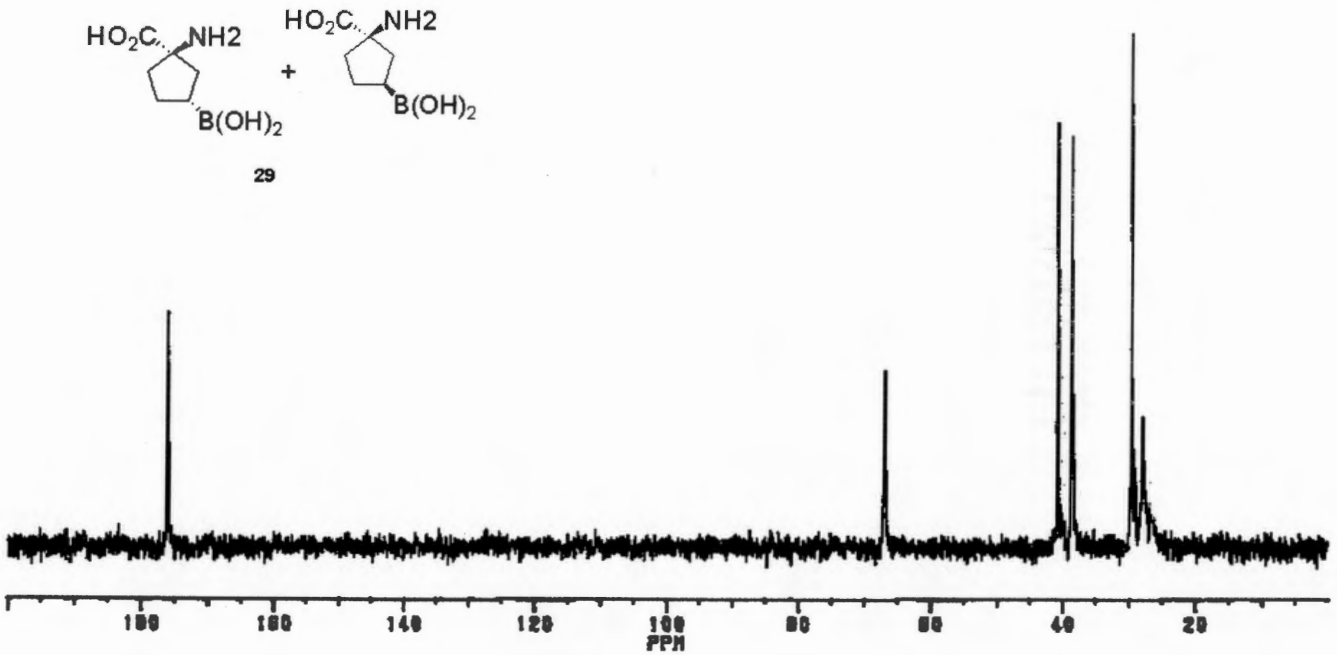

HN
O
NH
O
B
O
O
+
HN
O
NH
O
B
B
O
O
27
11
10
9
8
7
6
5
4
3
2
1

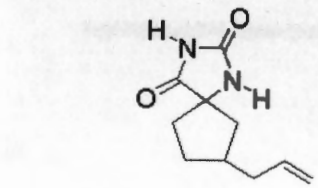

HN
O
NH
O
B
O
O
+
HN
O
NH
O
B
B
O
O
27
180
160
140
120
100
80
60
40
20
PPM


HO2C
NH2
B(OH)2
+
HO2C
NH2
B(OH)2
28
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

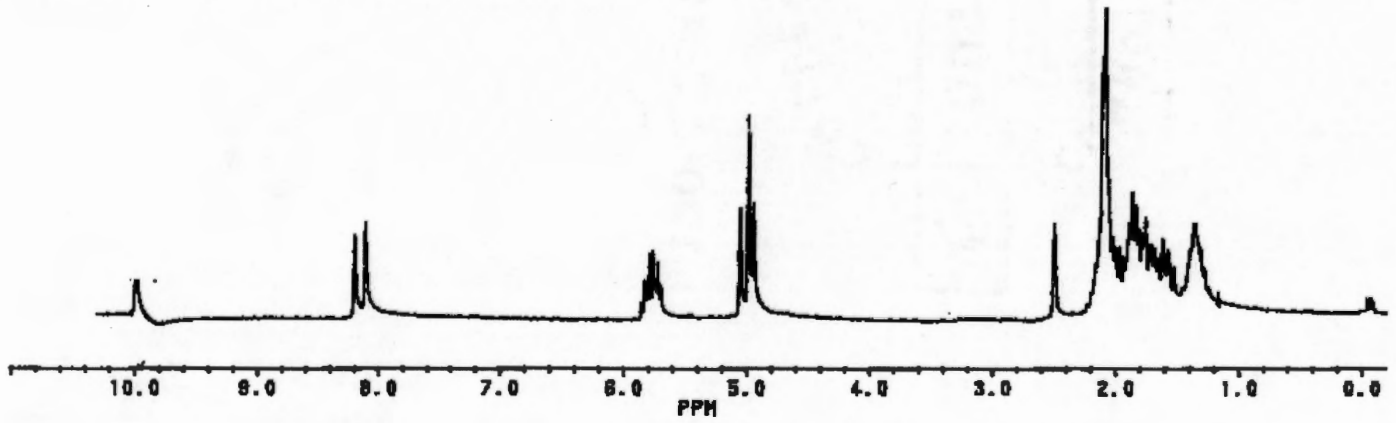

HO2C
NH2
B(OH)2
+
HO2C
NH2
B(OH)2
28
180
160
140
120
100
PPM
80
60
40
20

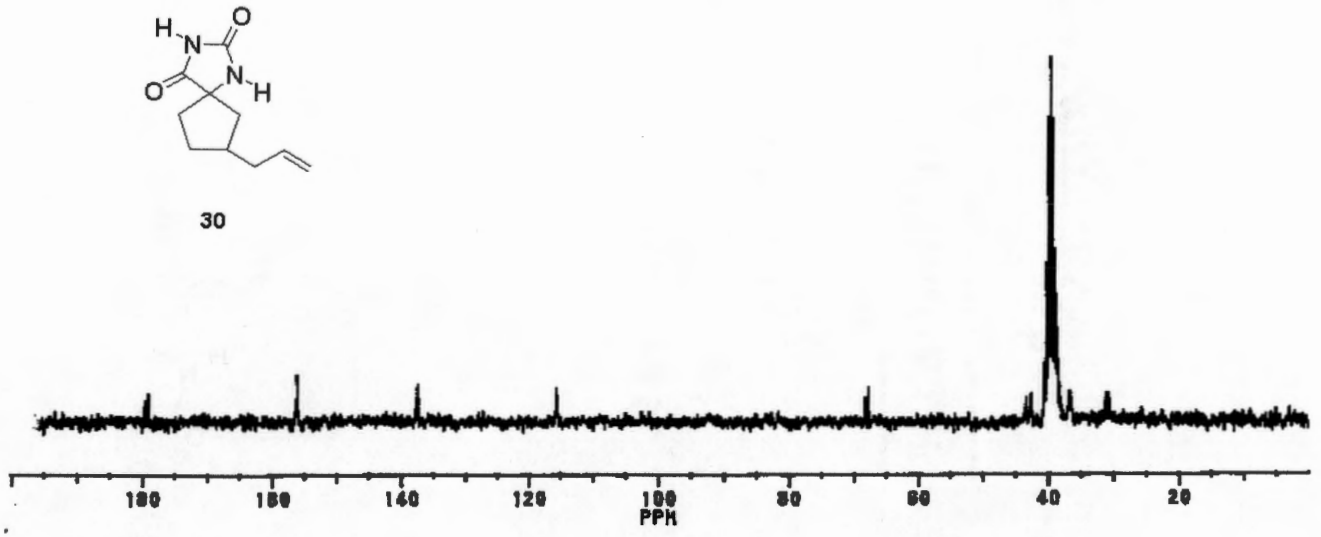

HO2C
NH2
B(OH)2
+
HO2C
NH2
B(OH)2
29
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

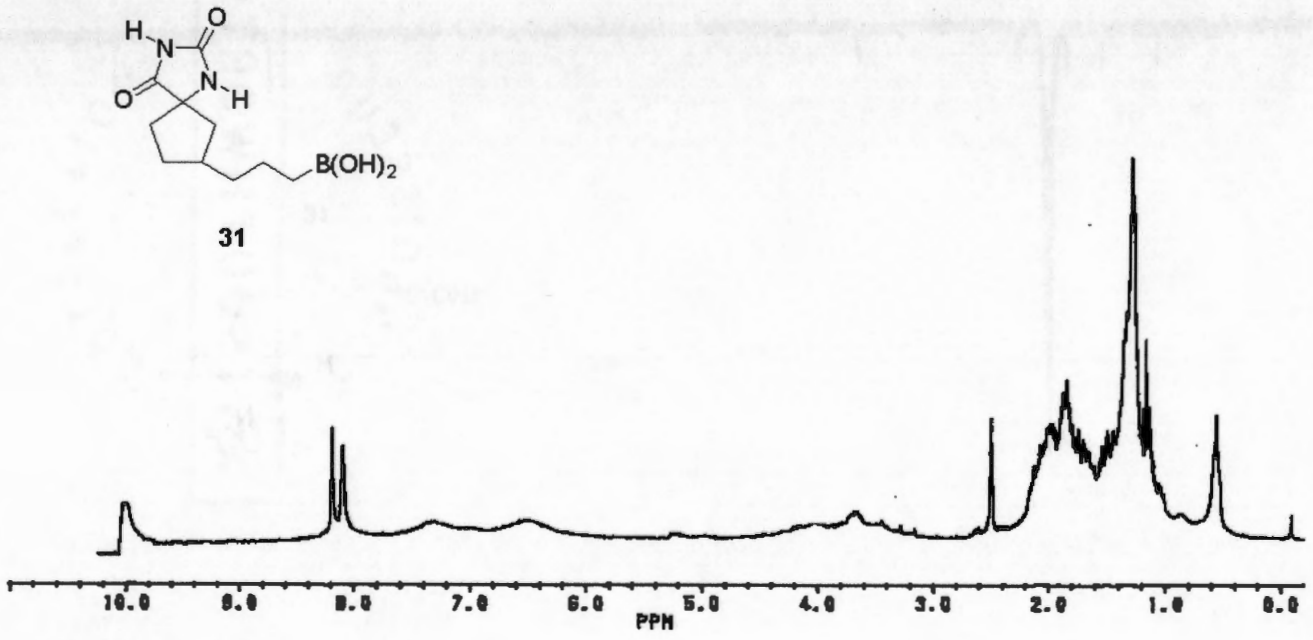

HO2C
NH2
B(OH)2
+
HO2C
NH2
B(OH)2
29
160
140
120
100
80
60
40
20
PPM



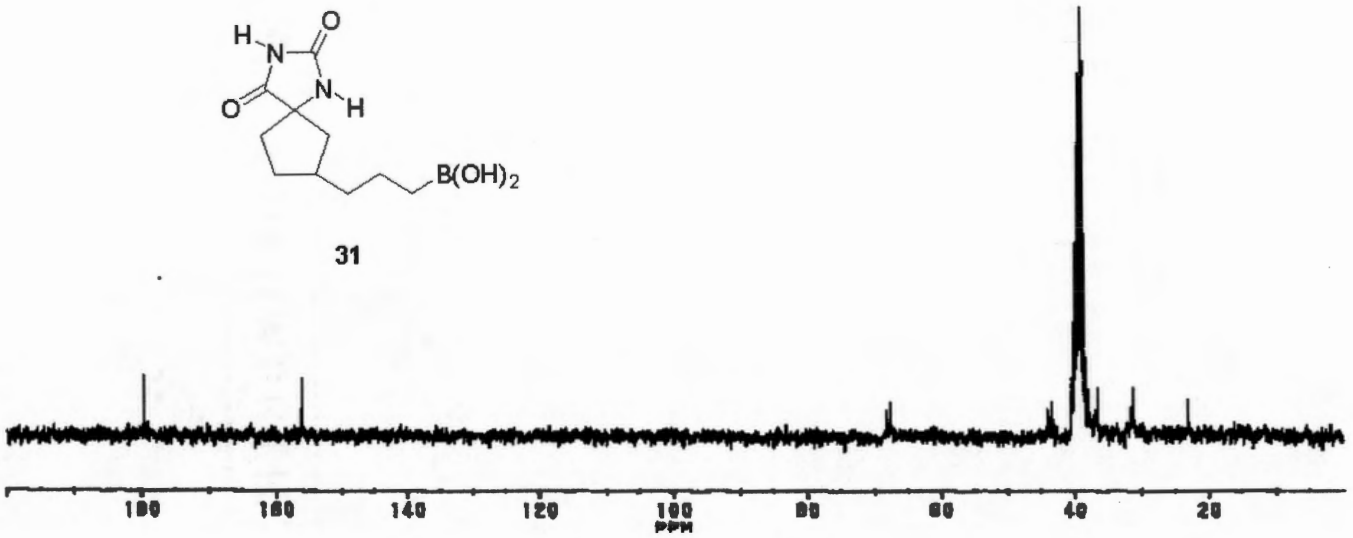
30

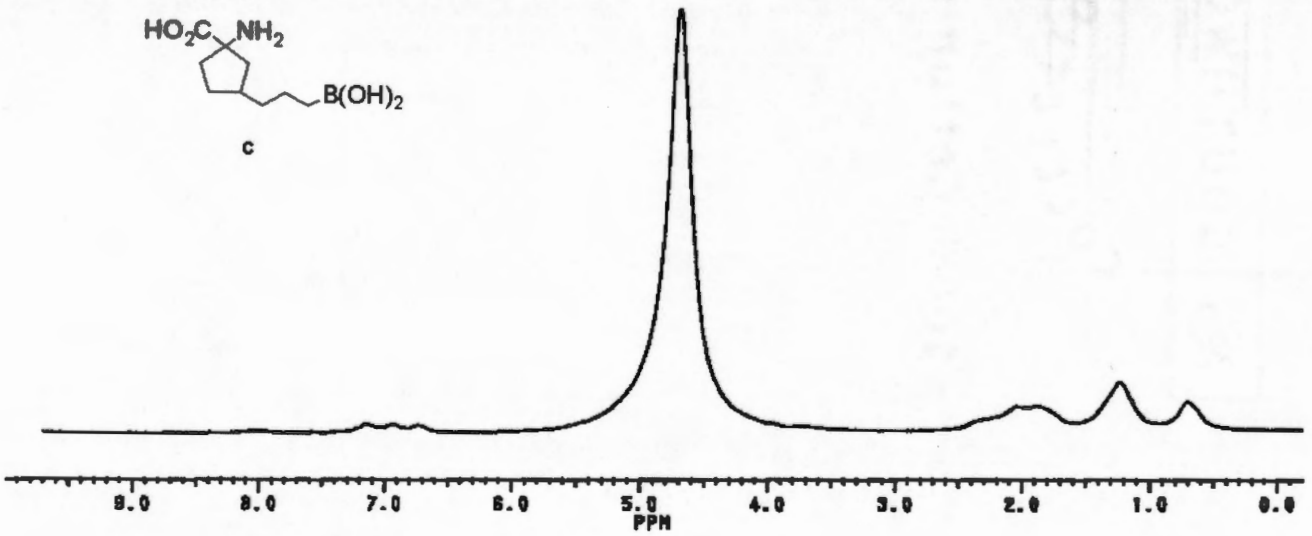


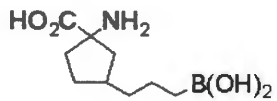

H
N
O
N
H
O
30
180
160
140
120
100
PPM
80
60
40
20



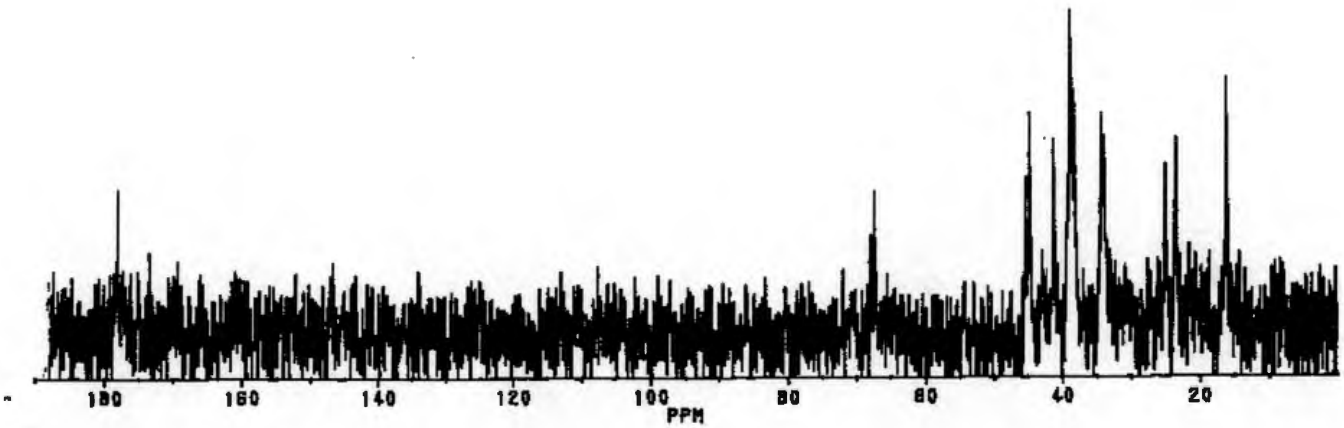

31


H
N
O
O
N
H
B(OH)2
31
180
160
140
120
100
80
60
40
20
ppm

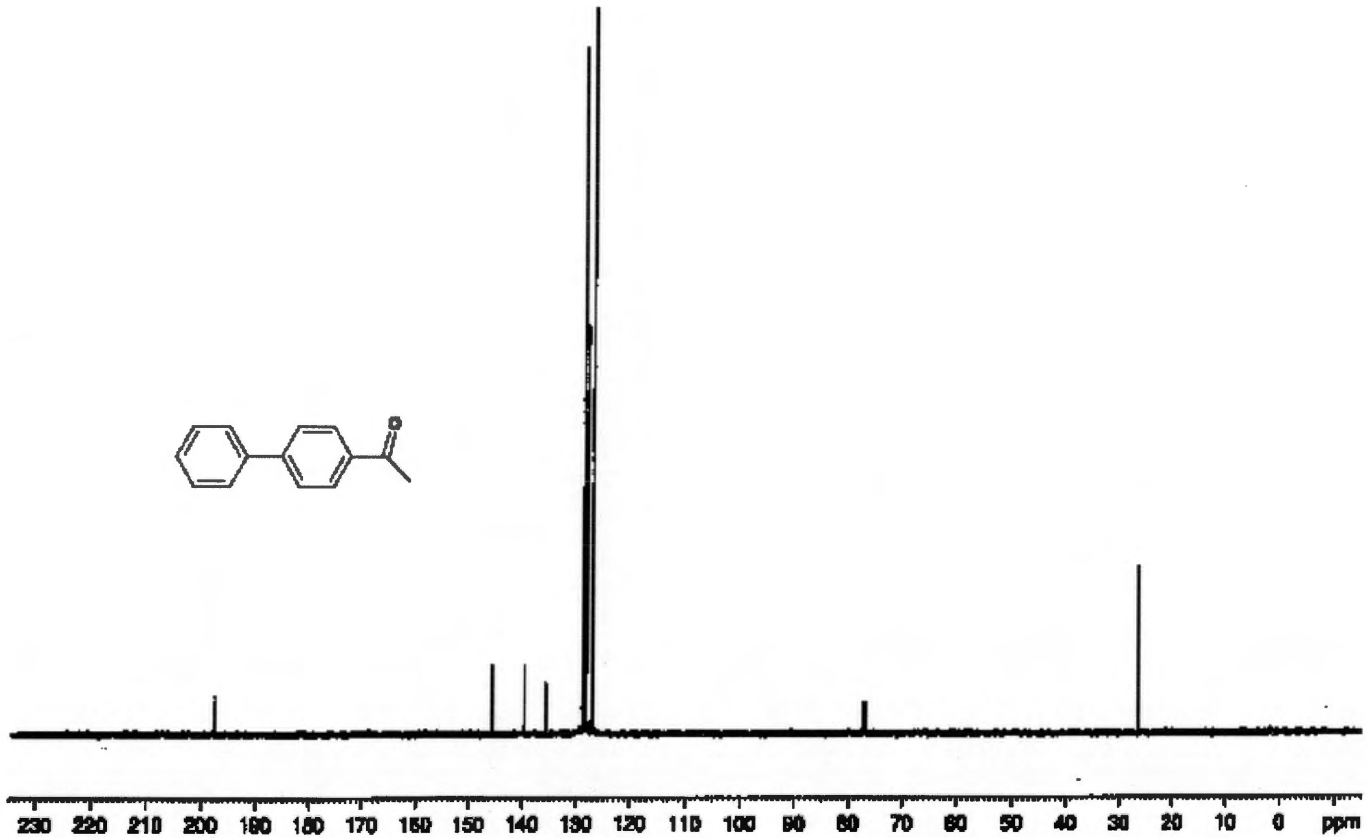

HO2C
NH2
B(OH)2
c
9.0
8.0
7.0
6.0
5.0
PPM
4.0
3.0
2.0
1.0
0.0

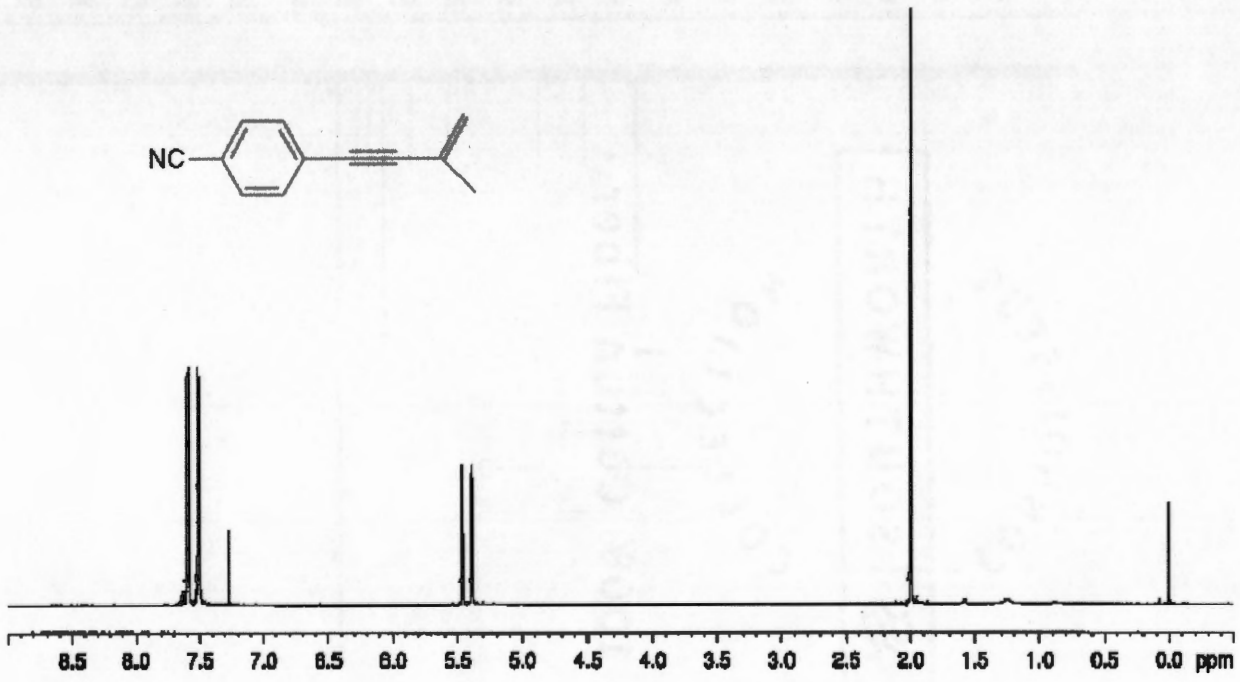


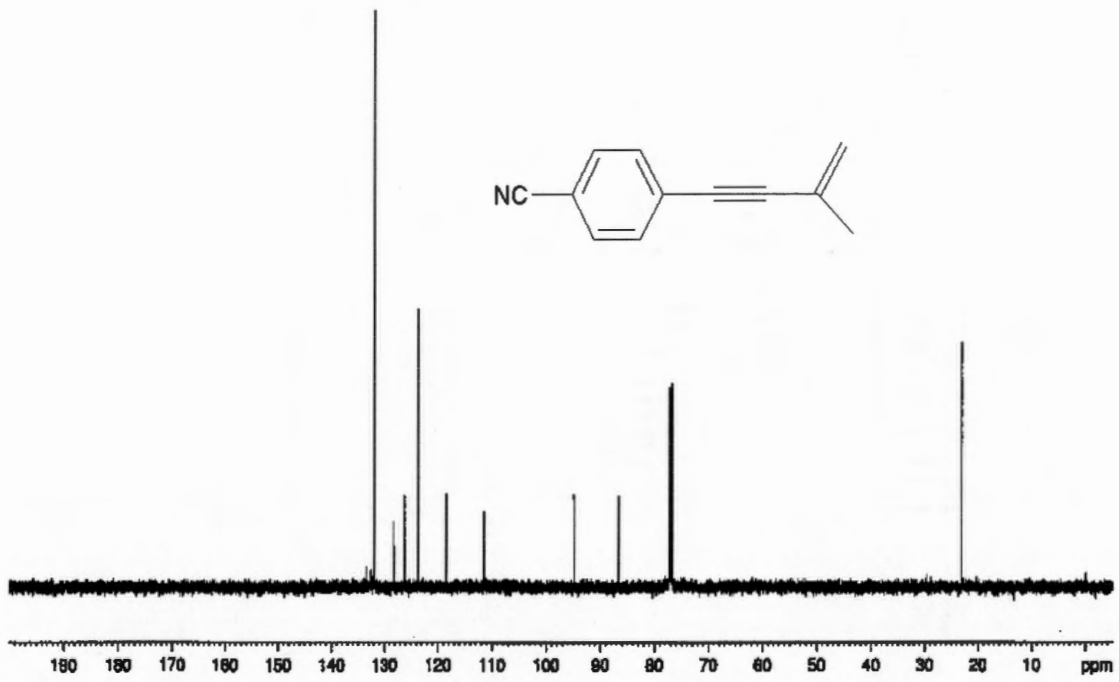

c

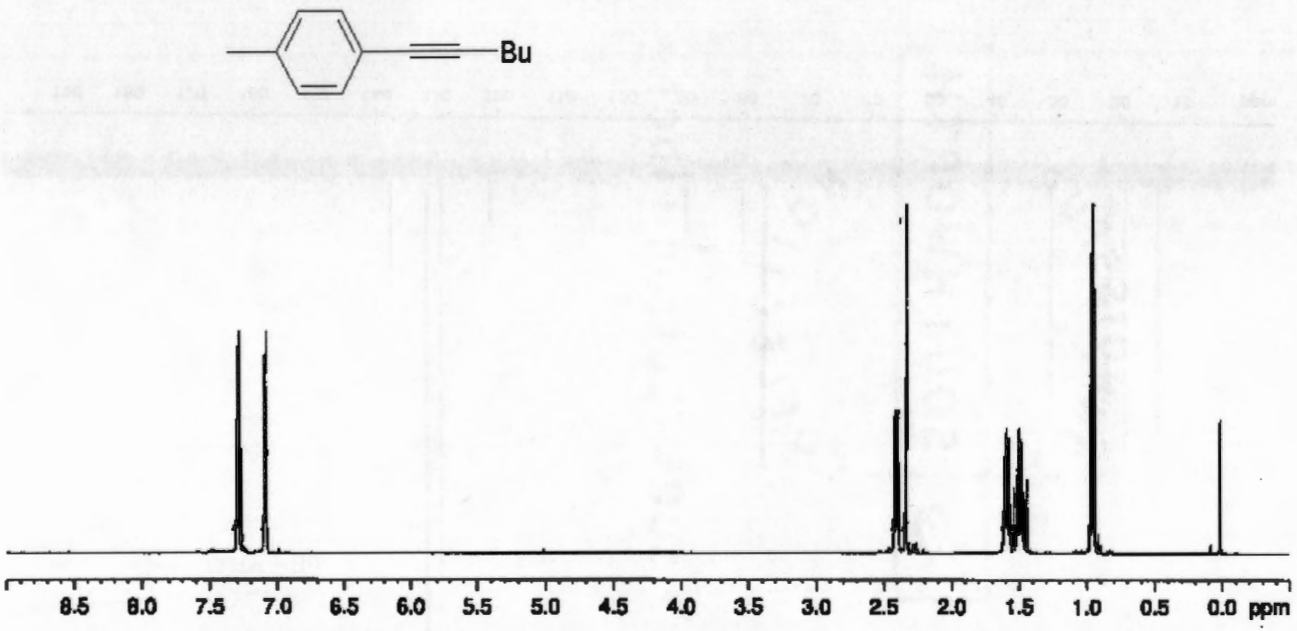


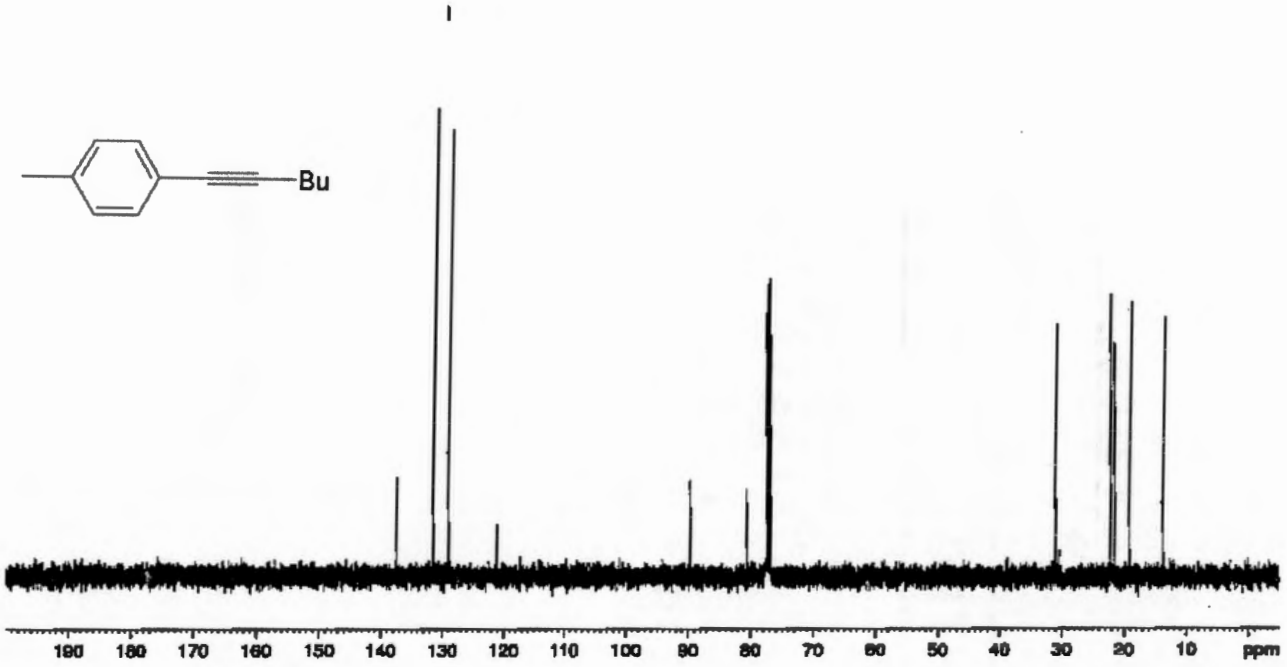
O
8
7
6
5
4
3
2
1
0

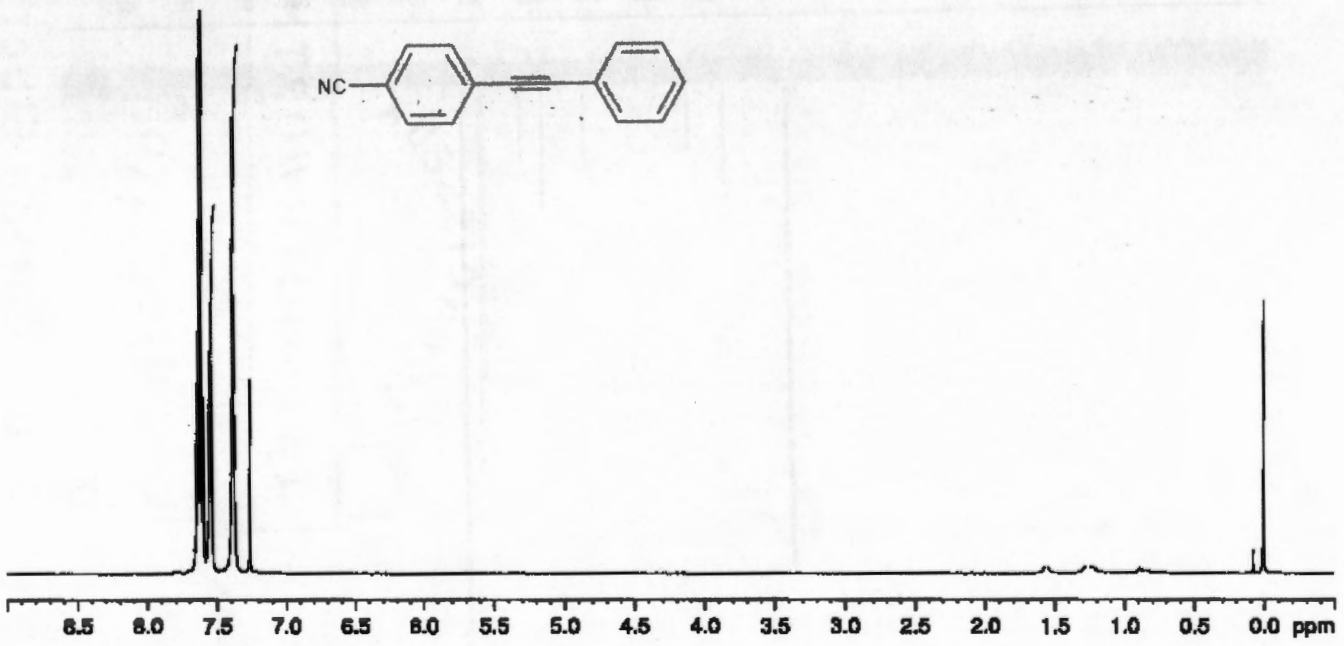

O
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

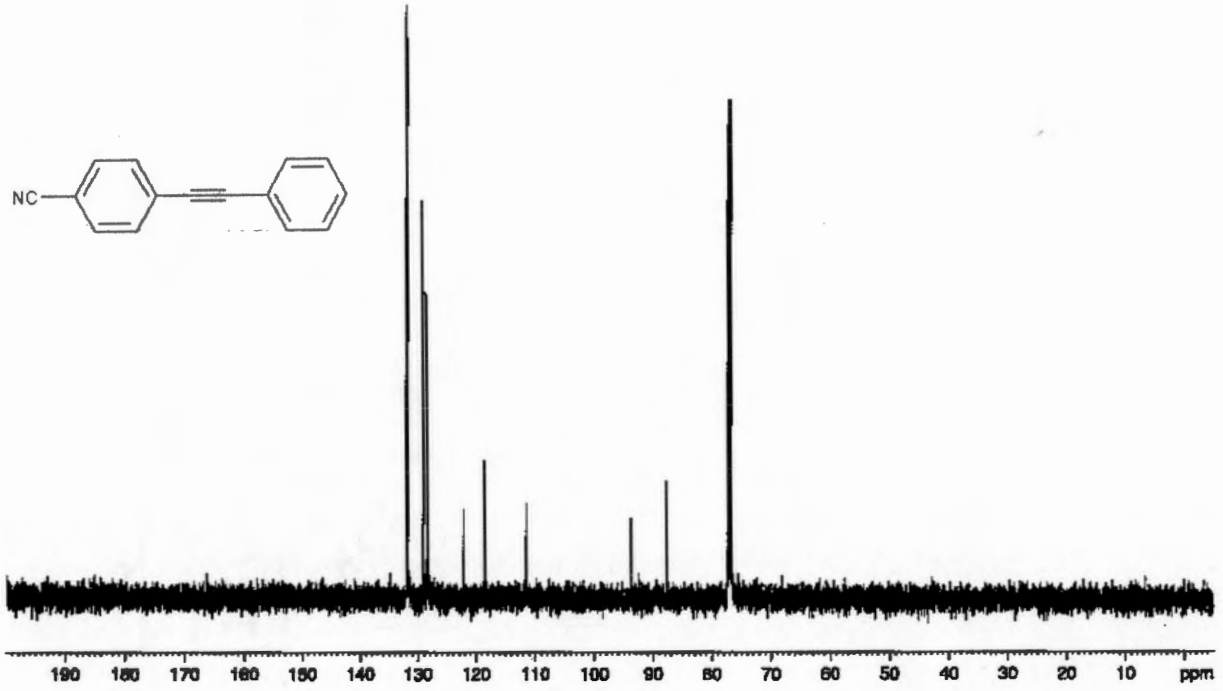

NC
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0 ppm

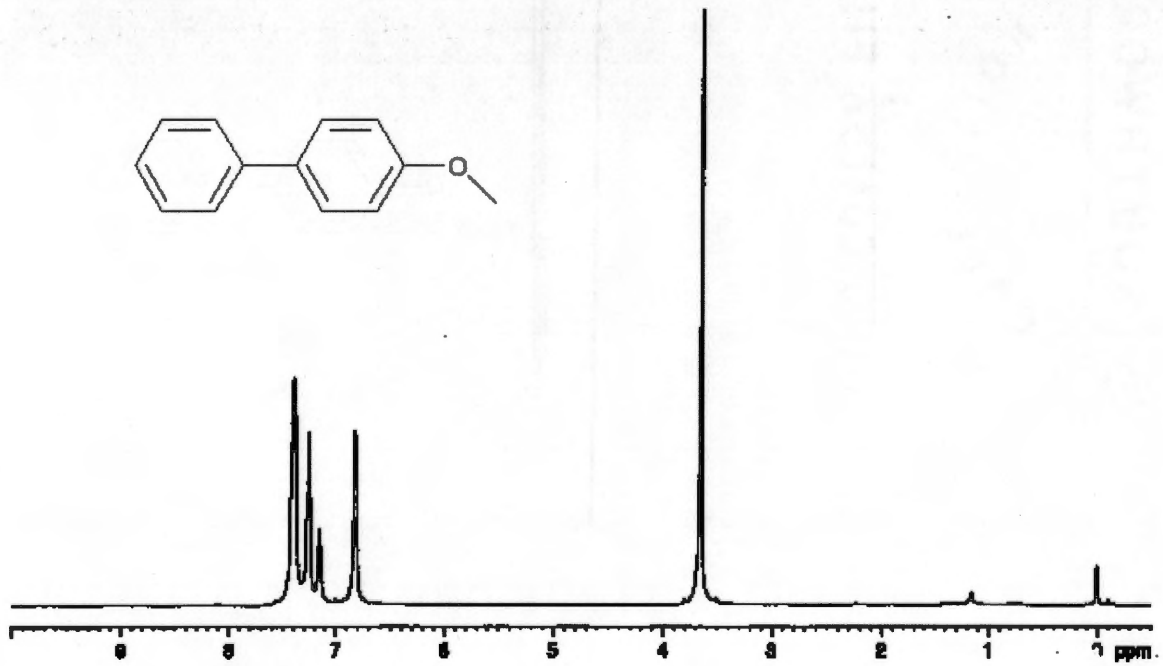

NC
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

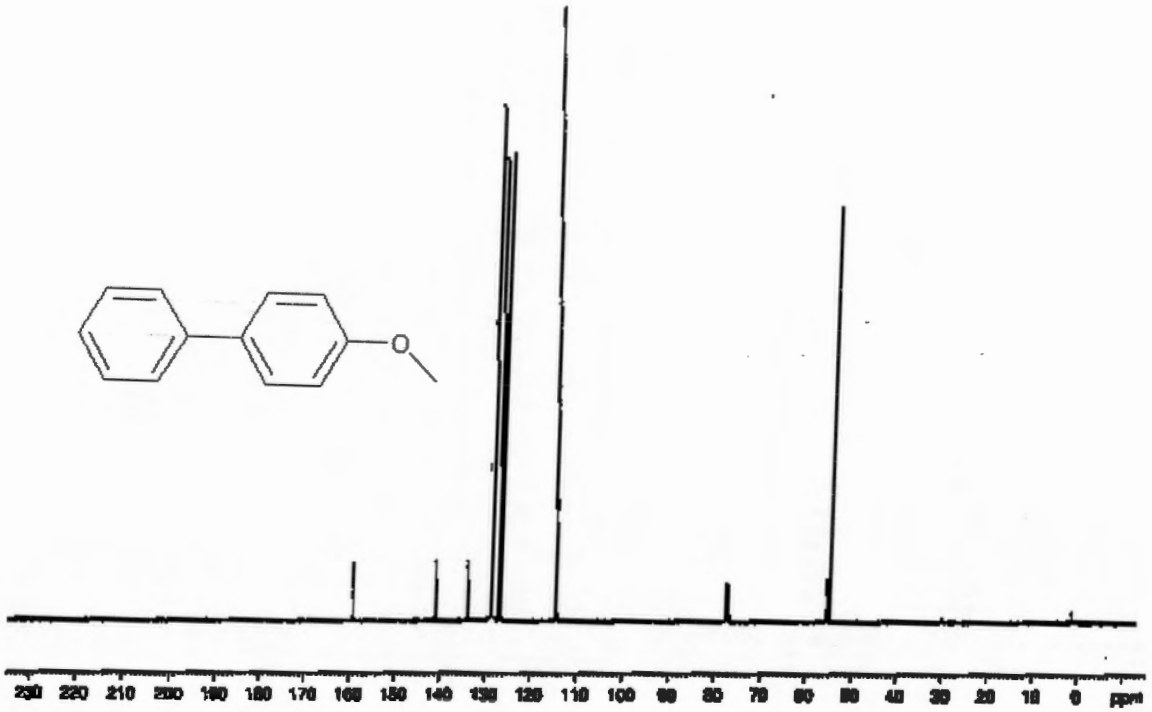

Bu
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

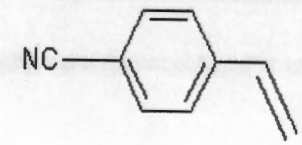

Bu
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

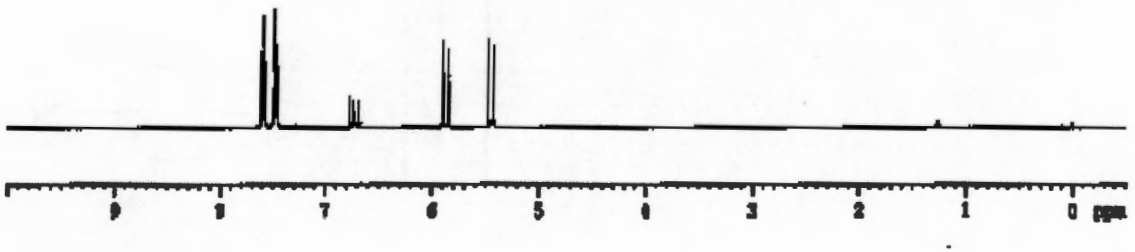

NC
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0 ppm

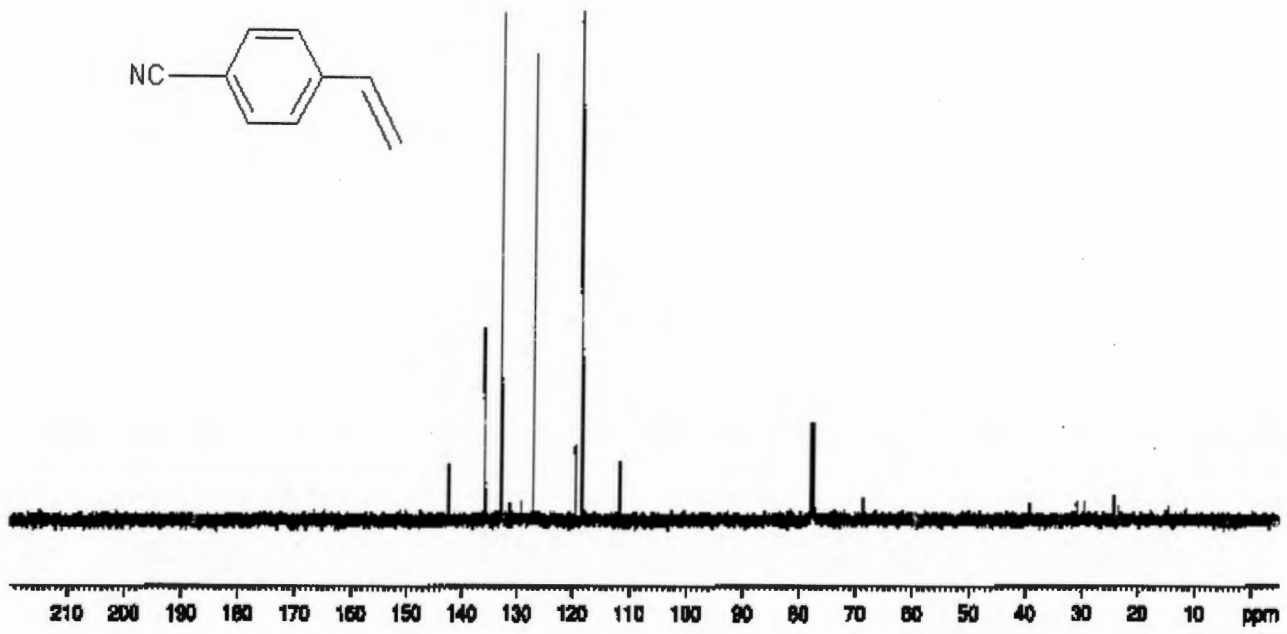

NC
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
8
7
6
5
4
3
2
1
ppm

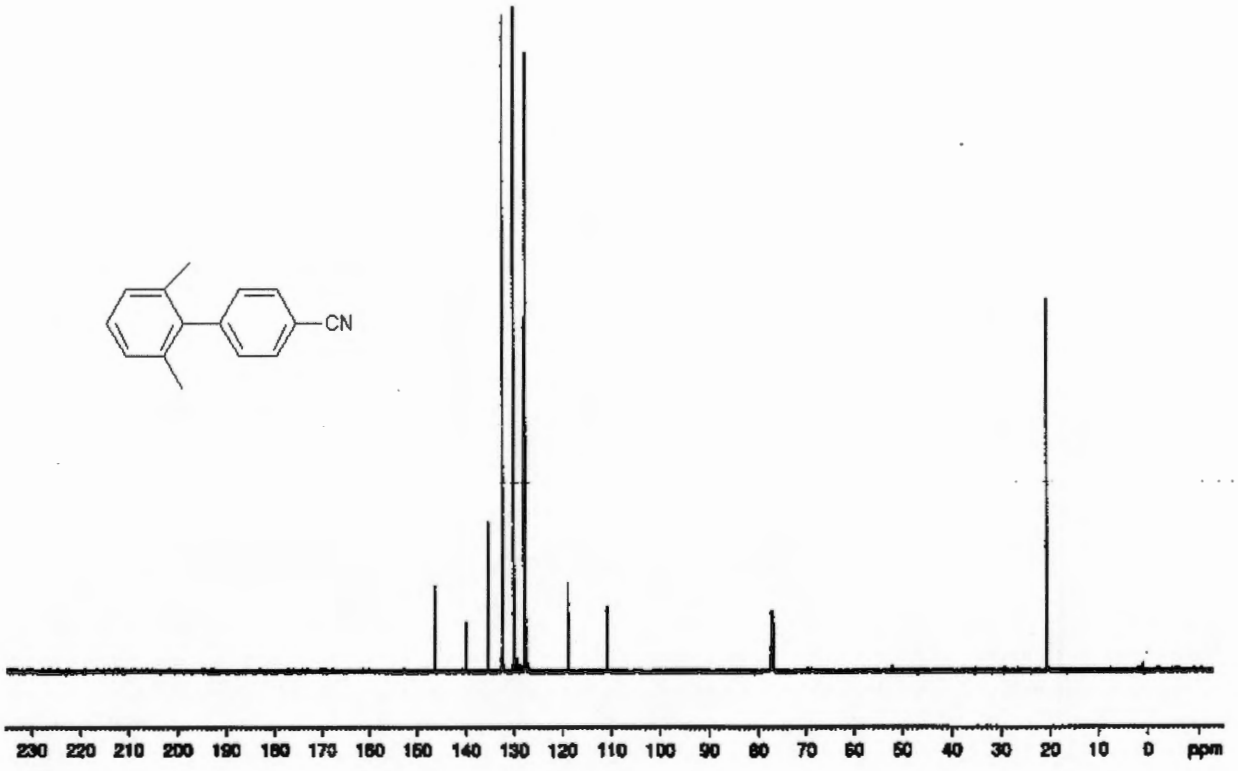

O
250 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


NC


8
7
6
5
4
3
2
1
0 ppm


NC
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

CN
ppm
0
1
2
3
4
5
6
7
8
9


CN
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

## Vita

Abhijit A. Naravane was born in Bombay, India on November 14, 1978. He received the Master of Science degree in 2002 from the University of Mumbai, with major in Organic Chemistry. In August 2003, he joined the University of Tennessee, Knoxville and received the Doctor of Philosophy Degree in Chemistry in 2007.